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THE JOURNAL OF INDUSTRIAL HYGIENE

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THE CONSEQUENCES OF MYOPIA AS AN INDUSTRIAL DISEASE OF THE EYES*

N. BISHOP HARMAN, M.A., M.B. (CANTAB.), F.R.C.S. (ENG.)

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THE outstanding feature of work in London is the immense amount of close eye work involved both in clerical positions and also in professional and technical work, such as that done by teachers, dentists, compositors, and skilled manual workers at the bench. It is a matter of common observation that continuous close work engenders fatigue, and that the liability of damage to the eyes is increased where there exist errors of refraction or of muscle balance. In some cases there occurs a breakdown in the ability of the worker to continue his work, and this results in a loss to the worker himself, to the employer, and to the community. Besides the liability to breakdown there is a lesser degree of crisis, one which makes the worker less efficient in his job; he continues at work, but the work done is inefficient as compared not only with his own standard under previous conditions of health, but also with the standard of other normal workers. Workers who have experienced either breakdowns or impairment in their ability desire to obtain a change of work if possible, even at some loss of earning power. For the most part, however, they return to work after an interval of rest, and, by reason of their physical disability, join the group of inefficient workers who follow a "ca' canny" policy.

The economic loss and the suffering involved in these cases, and the unhappiness which failure engenders in the mind of willing workers, are so great that we should attempt to prevent them. By suitable means persons likely to fail could be picked out before they made a choice of their life work, and their energies could be diverted into more promising channels.

In presenting evidence before the Committee on the Causes and Prevention of Blindness in 1920[1], I gave an account of the causes of blindness in 925

*This paper was read at the Congress of the Ophthalmological Society of the United Kingdom, May, 1922. Received for publication July 5, 1922.

[1] Harman, N. B.: The Causes and Prevention of Blindness, Based upon an Analysis of 4,288 Cases. *Brit. Med. Jour.*, 1921, *2*, 727.

private patients, and showed that the consequences of high myopia, over 10 D, accounted for 13.93 per cent. of blindness, thus occupying the second highest place among all causes of blindness, and the highest among irremediable causes. Very many of these patients had been engaged in clerical work during their working life.

In order to determine whether myopes engaged in continuous close work are exposed to any greater liability to breakdown or grave defect of vision than are myopes not engaged in such work, I investigated the records of about 7,000 private patients. These patients were from all classes of life and from varied occupations. From these records there were picked out all the myopes of over 3 D who were between the ages of 20 and 60 years. Cases of congenital defect, accident, or disease unconnected with myopia, and of monocular myopia were excluded. The total number of myopes thus collected was 480—quite a sufficient volume of material to allow reasonable inferences to be drawn. They were separated into two main sections: (1) habitual close eye workers; and (2) those not thus engaged. In each section there was an age grouping in decades, and also a grouping according to the grade of myopia—from 3 to 5 D, from 5 to 10 D, and over 10 D. In cases of astigmatism the average of the four meridians was taken as the degree of myopia. Note was made of the events of the patient's working history; of the occurrence of indications of abnormal stress in work; of breakdowns which entailed cessation of work, or change of work where that was possible, or a continuance of the same work under modified conditions; and, lastly, of direct evidence of damage to the eyes. The results thus obtained from the examination of these patients and from the comparison of the two sections — the habitual close eye workers and the other patients who were not close eye workers — are presented in Tables 1 and 2.

Of the 480 myopes whose records were investigated, 38 per cent. were engaged in habitual close eye work, and 62 per cent. were other patients not occupied in continuous close eye work. The higher percentage of the second group is accounted for by the fact that it included a large number of married women, and also most of the very high myopes who were prohibited from doing close eye work. The extent of failure among the habitual close eye workers as compared with the other patients is remarkable. No less than 53 per cent. of the close eye workers failed at some time during their career; of these, 15 per cent. sustained permanent damage through the loss of an eye; and two persons lost the sight of both eyes. Among the other patients failures were few, only a total of 9.4 per cent.; but among these the greater number, 7 per cent. (these were very high myopes), sustained damage to their

TABLE 1.—GROUP COMPARISON OF PERSONS HABITUALLY ENGAGED IN CLOSE EYE WORK AND OF PERSONS NOT SO ENGAGED

Type of Patient	Number	Breakdowns	Damage to Eyes	Total of Failures
Habitual close eye workers	183	70	27	97
	100%	38.2%	15%	53%
Other workers	297	7	21	28
	100%	2.4%	7.06%	9.4%
Total % in 480	100%	16%	10%	26%

eyes; four of these persons lost the sight of both eyes.

The second table shows that there was a gradual increase in the incidence of breakdowns and damage to the eyes with the increase in age and in the grade of myopia. In the group of patients not engaged in close eye work there was only one case of damage to the eyes and no instance of breakdown at any age among those with myopia of less than 5 D. Among the habitual close eye workers with myopia of less than 5 D, however, there were a number of cases of breakdown, and a few instances of damage to the eyes. The number of cases of breakdown and of damage increased rapidly for the close eye workers with 5 to 10 D of myopia, for it was in this group that they were most numerous; but there were only a few failures among the other patients with the same degree of myopia.

Breakdowns and damaged eyes (except for the age group, 50-60) were more numerous among the habitual close eye workers, but it will be noted that there was a higher rate of damaged eyes than of breakdowns among the other patients. This is accounted for by the fact that this section contained most of the very high myopes, who had been warned against doing close work, and many of whom had doubtlessly been saved by attention to this warning. Some of them had such high degrees of myopia, however, that damage was almost inevitable.

The character of the damage sustained was as follows: detachment of the retina, 14 cases; degeneration of the macular region, 34; gross vitreous hemorrhages and the damage consequent thereon, 5; rapid myopic cataract, 3. It is noteworthy how much more serious is the risk of loss of central vision from degeneration of the macula in these myopes, than is the risk of detachment of the retina. Happily, loss of the macula does not leave them in

TABLE 2.—COMPARISON OF HABITUAL CLOSE EYE WORKERS AND OF PERSONS NOT SO ENGAGED, GROUPED ACCORDING TO AGE AND TO GRADE OF MYOPIA

Ages	20-30			30-40			40-50			50-60			Totals for Type and Degree of Myopia		
Degree of Myopia and Type of Patient	Number	Breakdowns	Damaged	Number	Breakdowns	Damaged	Number	Breakdowns	Damaged	Number	Breakdowns	Damaged	Number	Breakdowns	Damaged
3 to 5 D															
Habitual close eye workers	30	8	—	21	9	1	11	2	1	9	2	1	71	21	3
Other workers	43	—	—	25	—	—	31	—	—	17	—	1	116		1
5 to 10 D															
Habitual close eye workers	30	14	2	26	14	2	13	7	2	12	5	3	81	40	9
Other workers	32	—	1	27	1	1	33	1	1	26	1	1	118	3	4
Over 10 D															
Habitual close eye workers	5	1	3	9	2	4	9	4	4	8	2	4	31	9	15
Other workers	11	—	—	15	1	2	16	—	4	21	3	10	63	4	16
Totals for ages	151	23	6	123	27	10	113	14	12	93	13	20	480	77	48

such a hopeless state as does detachment of the retina. Only six cases of total loss of vision in both eyes were recorded; but in many other cases with the total loss of central vision of one eye, there was also a considerable diminution of the vision of the other eye from the same condition of macular degeneration.

The work done by some of the habitual close eye workers was sometimes of an incredible nature. One person with 17 D of myopia was engaged as a printers' proofreader and corrected statistical tabular matter all day long; another with 12 D was a miniature painter; and yet another with 10 D was a dental mechanic. Some of the close eye workers had made a change of work on their own account: two lawyers forsook their clients, one to become a farmer, the other to become a cinema controller; the miniature painter took over the management of a depot; and the mechanical dentist became a shop assistant. The proofreader, however, preferred to continue and take the risk.

The lesson of these figures is plain enough. No matter what view we may hold of the causes of myopia, it is certain that the risks of myopia are heaviest with the patients whose occupations entail habitual close eye work. The liability of damage to one or both eyes in close work is so great that we are in duty bound to prevent young people, who are affected by myopia of more than the lesser grades, from entering work of this kind; otherwise, a high percentage of them may sustain partial blindness.

THE COMPARATIVE EFFICIENCY OF THE CIRCULAR KONIMETER AND THE PALMER WATER SPRAY APPARATUS FOR THE DETERMINATION OF THE DUST CONTENT OF THE AIR*

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Introduction

Aside from the Palmer water spray sampling apparatus (1), the two other devices in general use in the United States for the determination of the dust content of air have been the sugar-filter method and the Hill dust counter. The latter method collected only the very large particles, and the former was difficult to use with accuracy, so that the Palmer apparatus was recommended for general use in 1917 by the Committee of the American Public Health Association on Standard Methods for the Examination of Air (2), and has been extensively utilized by many observers since that date.

During the last few years notable improvements have been made in the sugar filter (3) (4), chiefly by the use of a container holding a much larger volume of the filtering medium. Meanwhile, also, the experts of the Miners' Phthisis Prevention Committee of South Africa (5) have introduced a new device, the konimeter, which is an impingement method like that of Hill, but immensely superior, because it involves the use of an air current of sufficient velocity to secure the retention of the fine particles of dust which are not held back by the dust counter.

In view of these recent advances, it seems important that the whole question of atmospheric dust analysis should be reconsidered, and a careful comparison made of the efficiency of the several devices now available.

Apparatus Used in the Present Investigation

The investigation here reported involves a comparative study of the Palmer water spray apparatus and a South African konimeter of the new circular type. The Palmer apparatus was of the usual design now so familiar that it requires no comment. The konimeter was of the type described by Katz and Trostel (4), and was constructed by A. F. H. Devers, an instrument maker of Johannesburg.

Measurements of the area of the impinging orifice were made with a micrometer microscope. From the average of nine readings of the diameter the area was calculated to be 0.271 sq. mm. The average of nine observations of the diameter of the piston was 1.767 cm. By means of a needle pointer attached to the bottom of the piston, and a millimeter scale the actual travel of the piston was found to be 3.82 cm. From the diameter of the piston, given above, and the length of the stroke the volume of the cylinder was calculated to be 9.44 c.c.

According to the South African investigators the speed of the stroke should be sufficient to produce at the impinging nozzle an air velocity of 30 to 80 m. per second. Since the efficiency of this ma-

*Based on a thesis presented by the junior author in partial fulfilment of the requirements for the certificate in Public Health of Yale University. Received for publication Aug. 5, 1922.

chine depends on the velocity of the impinging jet, considerable attention was paid to this detail. The principle outlined in Appendix No. 3 of the Final Report of the Miners' Phthisis Prevention Committee of South Africa (5) was adopted. A strip of carbonized paper was fixed in a holder attached to the base of the piston. Resting against this paper was a pointer attached to a tuning fork making 100 vibrations per second. When the fork was caused to vibrate and the piston was released, a curve was produced on the smoked paper. The number of complete vibrations here indicated was equal to the time in hundredths of a second taken for the complete travel of the piston. The length of time required was found in this manner to be 0.70 seconds. This gives at the impinging orifice a velocity of 49 m. per second.[1]

After the calculated velocity and volume of the instrument had thus been obtained, it seemed best to check the volume by actual measurements. A small brass tube was screwed on the outer end of the impinging orifice; over this joint a small section of rubber tubing was fitted and the ends were made tight with sealing wax. The lower ends of two 10 c.c. pipettes were connected with rubber tubing and the upper end of one joined to a glass stopcock and then to the tube fixed on the konimeter. Sufficient water was placed in the apparatus to fill the open pipette and the connecting tubing. Pressure tubing was used and the top of the closed pipette was kept moist. That no leakage occurred could be shown by raising the water level in the closed pipette above that in the open pipette, closing the stopcock and observing the level for half an hour. The fact that the water level remained stationary during this interval indicated that the joint was air-tight.

After the konimeter had been set, the apparatus was connected and the open pipette adjusted so that the water in both tubes was brought to the same level. This level was noted. The konimeter piston was then released, and the water was permitted to rise in the closed arm of the U-tube. During motion the surface of this column was slightly convex. It was found that at the end of the stroke, when the pressure below the piston approximated that above it, leakage occurred around the piston packing, and the water level in the closed pipette could not be maintained till a leveling and reading could be made. The use of the stopcock removed this source of trouble. At the end of the stroke, at the instant that the raised center of the column began to drop, connection between the konimeter and the pipette was cut off by means of the stopcock. The open tube was then raised till the columns of water were again level, and the meniscus of the closed tube was read again. The difference between this reading and the first one gave the volume of air aspirated by the konimeter. If the piston was kept clean and lubricated with a slight amount of powdered graphite, little variation was observed. The average volume of air removed was 9.36 c.c., or 99.15 per cent. of the calculated volume.

When dust samples were taken in places where the air was exceedingly dusty, it was found advisable to reduce the amount of air sampled. In this manner the intensity of the dust spot was kept at such a value that the count could

[1] A new spring was obtained and tested in an effort to increase the velocity, but owing to the uneven rate of travel that it produced, it had to be discarded.

be made with a fair degree of ease. In order to accomplish this it was only necessary to reduce the travel of the piston, and for this purpose several small trapezoids of sheet brass were made. They were of such sizes that, when placed in the line of the piston travel, they would cut down the volume of the air sampled to approximately one-fourth, one-third, one-half, and two-thirds of the total volume of the cylinder. The volume of air sampled was carefully determined with the stops in place and was found to be 2.30 c.c., 3.13 c.c., 4.93 c.c., and 6.46 c.c., respectively.

Methods of Sampling

The bottles used for the Palmer samples were Erlenmeyer flasks. They were scrupulously cleaned in the laboratory and slightly more than 100 c.c. of distilled water placed in each. Heavy caps of wrapping paper were fastened over the rubber stoppers with rubber bands. On arrival at the place where the samples were to be taken the apparatus was set up and connected with an electric light socket. About 40 c.c. of water were then placed in the bulb. If the sampling was not started immediately the intake was protected by a small box cover. The manometer was leveled by means of the attached spirit level. After running for a definite length of time, usually twenty or thirty minutes, the water was drawn into a clean flask, the bulb rinsed two or three times, and the washings added to the sample. The bottles were then recapped and brought to the laboratory.

The circular glass of the konimeter, after being washed, was carefully cleaned with lens paper and was then smeared with a thin layer of white vaseline, by means of a glass rod. The vaseline prepared for medicinal purposes was found quite free from dust, and the small tubes in which it may be purchased are convenient to use. The slide, after being vaselined, was examined under the microscope to make certain that it was free from dust. It was then placed in the konimeter and the face plate screwed on. While we were in the places where samples were taken, it was kept in a small carrying case, except for the few seconds necessary to set and release the plunger and to turn a new surface in place before the orifice, by means of the screw provided for that purpose. A sample was taken at the moment that the Palmer apparatus was started, and every five minutes thereafter throughout the time of Palmer sampling. The only exception to this was in Series D, where the extreme conditions made it impracticable to run the Palmer apparatus over eight minutes, and here konimeter samples were taken at correspondingly shorter intervals. Also in Series D, which consists of very high counts, one of the stops previously mentioned was used in all samples.

General Results

In all, thirty-five Palmer air samples were studied in the present investigation, distributed as follows:

Series A.—Knife-handle grinding and polishing shop (coca-bola wood mainly)	9
Series B.—Plier grinding shop	8
Series C.—Quiet air in unused laboratory	8
Series D.—Sand-blasting room	10

The general results are indicated in Table 1. It is evident that the konimeter gives far higher results than the Palmer apparatus. In Series A (wood dust) the ratio of the konimeter count to the Palmer count varied for individual samples from 4.8 to 9.8, and averaged

7.3; in Series B (metallic dust) it varied from 18.2 to 33.8, and averaged 23.4; in Series C (normal air) it varied from 7.0 to 58.0, and averaged 19.5; in Series D (heavy silicious dust) it varied from 1.7 to 7.5, and averaged 2.8.

TABLE 1.—COMPARATIVE DUST COUNTS OBTAINED WITH KONIMETER AND PALMER APPARATUS

Series		Particles per Cubic Foot	
		Konimeter	Palmer Apparatus
Series A	Minimum	852,000	110,900
	Average	2,054,500	281,000
	Maximum	3,377,000	470,000
Series B	Minimum	3,389,000	101,500
	Average	4,882,500	208,000
	Maximum	9,410,000	343,900
Series C	Minimum	270,500	25,800
	Average	733,500	37,500
	Maximum	1,660,000	54,200
Series D	Minimum	6,660,000	2,130,000
	Average	40,676,000	14,394,000
	Maximum	91,500,000	38,650,000

Relative Efficiency of the Two Procedures with Reference to Particles of Different Sizes

In Table 2 are presented data for the konimeter-Palmer ratio, with distinction in regard to the size of the particles counted. It appears that with the particles of a diameter over 10 microns the konimeter is from two to three times as efficient as the Palmer apparatus (with the heavy dust of Series D it gave a lower count than the Palmer). For the particles less than 10 microns in diameter, on the other hand, the konimeter is far more efficient, showing a count from ten to twenty times higher than the Palmer count, except in the case of the sand-blast dust where the two methods were more nearly alike.

It seems clear that the ratio between the konimeter and the Palmer count is primarily conditioned by the size of the particles involved. In Series A and Series D, which showed average ratios under 8, over fifteen particles in 1,000 of the dust were over 10 microns in diameter. In Series B and C, in which the konimeter-Palmer ratio was from 19 to

TABLE 2.—RATIO OF KONIMETER TO PALMER COUNT FOR PARTICLES OF DIFFERENT SIZES

Series	Type of Dust	Ratio for Particles		
		Under 10 Microns	Over 10 Microns	All Particles
A	wood	8.9	2.1	7.3
B	metallic	24.1	3.8	23.4
C	normal room	20.0	3.5	19.5
D	heavy silicious	2.9	0.9	2.8

23, less than five particles in 1,000 of the dust particles were over 10 microns in diameter.

Since it is the particles under 10 microns in diameter which are of major sanitary significance, the superiority of the konimeter seems to be reasonably clear.

Sampling Error Involved in the Use of the Konimeter

The fact that the konimeter takes a so-called "instantaneous grab sample" obviously offers considerable possibilities of error in its use. It has already been pointed out that in the present study each konimeter count used for comparison with a Palmer count was based on the average of three to seven individual konimeter fields, a konimeter sample being usually collected every five minutes during the period of the Palmer sampling. Of 198 individual konimeter samples but four showed a deviation of over 100 per cent. from the average of the sampling group to which they belonged, and but forty-two showed a deviation of over 50 per cent. When we consider the average deviation for a

group of konimeter samples taken during a single Palmer sampling procedure we obtain the following results:

3 group samples had an average deviation of	0–19%
21 group samples had an average deviation of	20–39%
9 group samples had an average deviation of	40–59%
1 group sample had an average deviation of	60–79%
0 group sample had an average deviation of	80–99%
1 group sample had an average deviation of	100–119%

On the average, therefore, even a single konimeter sample will generally give a result within 60 per cent. of the average of a series of such samples collected at the same place and at approximately the same time. It would be well, in practice, to take three konimeter samples at a given point at intervals of five minutes, a procedure which would yield entirely representative results with far less labor than that involved in the collection of a single Palmer sample.

Summary and Conclusions

1. It appears from this study that the circular konimeter gives dust counts from two to twenty times as high as those obtained with the Palmer apparatus.

2. The finer the dust, the greater is the excess of the konimeter count over the Palmer count, a fact which weighs heavily in favor of the konimeter, since it is the fine particles which are of chief sanitary significance.

3. Sampling errors due to the small volume of air collected by the konimeter do not appear to be serious. They can be reduced to a negligible value by taking three konimeter samples at a given point at intervals of five minutes.

4. The konimeter is altogether superior to the Palmer apparatus in regard to portability and to economy of time and labor in sampling and counting.

5. It is evident that the whole problem of standard methods for determining atmospheric dust should be reconsidered. Before the konimeter or any other device can be substituted for the Palmer apparatus extensive examinations must be made of air from various types of industrial establishments, since the standards now in use in this country are based on the Palmer method and must be fundamentally revised before practical conclusions can be drawn from the use of any other procedure.

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THE RÔLE OF SYPHILIS IN INDUSTRIAL DISABLEMENT: ANALYSIS OF 291 PHYSICAL SURVEYS*

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THE physical surveys which are reported in this article were made for several reasons. A great many of them were requested by the relief department of a Baltimore company because of unsatisfactory diagnosis, especially in cases characterized by delayed convalescence and prolonged disability. Others were requested by the claim and legal departments in order to determine the extent and character of disablement, if any, for the purpose of settlement. The number of positive syphilitic findings was so great that our attention was attracted to this condition as one playing an important part in, and frequently the entire cause of the disablement.

The diagnosis of syphilis was based on the physical findings, blood and spinal fluid Wassermann test. In the Wassermann test used two methods and two antigens were employed: ice box and water bath methods; and cholesterine and alcoholic antigens. I realize that certain exceptions may be taken to the accuracy of the Wassermann reaction. Until some method without possible error has been developed, however, we must necessarily accept the Wassermann test as performed by an experienced and well-equipped laboratory as 100 per cent. accurate. Whatever error the test has, will be on the positive side, and someone may receive unnecessary treatment. When one considers the dire results from failure of early recognition and from insufficiency of treatment, one cannot but conclude that the minute degree of inaccuracy (less than 1 per cent.) may be ignored for the sake of the greatest good to the greatest number.

*Received for publication Aug. 10, 1922.

SUMMARY OF CASES

There were 291 surveys made. The blood was examined for syphilis in 222 cases, of which 187 gave negative results, and 35 positive results. In 69 cases early in the series, we did not make a Wassermann test as we did not then think that it was indicated. Had we done so, I believe that the total number of positive cases would have been larger. Of the total number of patients —that is, 291—we found that 12– per cent. had syphilis. Of those cases in which the Wassermann test was made —namely, 222—15– per cent. gave positive results. In the 35 cases of syphilis we found 32 positive blood Wassermanns, and 3 negative with positive spinal fluid. There were 14 positive spinal fluids, and 2 negative; in 19 cases the spinal fluid was not obtained. In 11 cases both blood and spinal fluid were positive. Twelve patients gave a definite history of syphilis. Nineteen had definite cerebrospinal syphilis; of this number, 14 were trainmen or had to do with the operation of trains; 6 were engineers; 1, a conductor; 4, brakemen; 2, firemen; and 1, a telegraph operator. Five other trainmen had chronic syphilis. Of the 35 patients

with syphilis, 15 are now permanently disabled; 15 are temporarily disabled; and 4 are dead.

The total amount of time which was lost by these thirty-five employees up to May 1, 1921, was 13,946 days; the largest number of days lost by one person was 2,003, the smallest, 30, making the average 410. The cost to the relief department for the same period was $25,296.10, the cost to the company as compensation, $25,415, making a total cost of $50,711.10.

While we are not in a position to say that syphilis was the sole cause of disablement in all these cases, we can say that where other conditions were complicated by syphilis the original disablement was prolonged directly by the disease, and without exception the problem in each case was to treat the syphilis as a primary means toward terminating the disablement. There were nine cases of injury in the list; the remainder were medical conditions, and of this group twenty-one were cases of definite mental disturbances.

There are several interesting and important questions arising out of a study of this sort. For instance, what measures can we take to help those already disabled; to prevent a continuance of this condition among employees; to guard the safety of the traveling public; and to protect the company property? There are three viewpoints from which the problem may be approached: that of the individual; that of the community and the employer; and that of the consultant physician. The individual will naturally ask: "If I have syphilis, why should there be any delay in making a diagnosis? Can I be cured? If an early diagnosis had been made, would it have had any bearing on the final result of the treatment? Am I a source of danger through contagion to my family or to the public?"

The viewpoints of the public and of the employer are the same, and have to do with the conservation of life, health, and property. The logical questions are again: What is the possibility of contagion? What effect does the disease have upon the capacity of the men as railroad employees? Did any of the workers have syphilis at the time of employment? Can syphilis be detected by the ordinary physical examination for employment? Is there any way of making an early diagnosis in persons acquiring the disease after the entrance examination? Can they be cured?

The medical viewpoint includes all of the foregoing problems with the additional problems of determining when patients cease to be contagious; when they are safe as trainmen; by what standards their fitness can be determined; in what way their entrance into the service can be prevented; how those acquiring the disease after entrance can be discovered; and how efficient treatment can be given those who are unable to pay for it.

In the following I shall attempt to answer these questions, though not categorically. The delay in making an early diagnosis of syphilis is due to laxity or insufficient observation on the part of the medical adviser. I believe that for the most part the failure is due to hurried and careless examinations. Most of these syphilitic cases are entirely under the care of the family physician. He passes on his diagnosis to the medical examiner, who accepts it without further inquiry, and the result is that the *patient* loses his only hope of cure. It must be remembered that in the vast majority of cases the medical examiner has no alternative but

to accept the diagnosis given, as he has no ethical reason for investigation until the disability has extended beyond a reasonable time. Then, in the interest of the relief department, as a mutual insuring agency, he is entitled to ask for further search for the cause of disablement. In trainmen, however, the danger to the life and property of the community demands that every case of suspicious illness — such as lapse of memory, failing vision, continued dizziness, erratic conduct, uncontrolled temper, and especially cases of employees who possess ideas of grandeur, and are prone to boast of their ability and possessions — should be investigated minutely, and syphilis should be borne in mind as a possible cause. Little credence should be given to the absence of positive history. All trainmen who have been disciplined for disobedience of orders in handling trains should not be permitted to return to work until a complete medical examination has been made. All cases of disablement of more than thirty days' duration, unless the diagnosis covering the condition is obviously correct, should be referred for a more complete examination. Certainly, disablement should not be permitted to continue indefinitely without a well-directed effort to arrive at a diagnosis, and thus prevent unnecessary and oftentimes fatal delay in instituting proper treatment.

Stokes and Brehmer, from the immense material of the Mayo Clinic, have reported in THIS JOURNAL[1] a study of syphilis which has a direct bearing upon this discussion. They reviewed the general medical examinations of 1,763 patients, and found syphilis, obvious enough to be detected without laboratory tests, in 3.1 per cent.; 4.2 per cent. of the men had the disease, and 2.6 per cent. of the women. The lowness of these figures coming from a well-equipped clinic emphasizes the weakness of clinical judgment alone, in the recognition of this disease, as compared with the diagnoses based upon the Wassermann test. Of the positive diagnoses, 58.7 were contributed by laboratory procedures. Of the railroad employees examined 11.7 per cent. had syphilis. The disease was eight times as frequent in them as in farmers (1.5 per cent.); three times as frequent as in business men (3.8 per cent); and twice as frequent as in laborers (6.1 per cent.). The doubtful value of the history of infection in the recognition of these cases is shown by the fact that 24 per cent. had no history of infection other than gonorrhea.

The only hope that we have of curing these patients lies in the early recognition and vigorous treatment of the infection. The sufficiency of treatment is to be determined by the blood and spinal fluid reaction, and no one should be discharged as cured until a negative Wassermann on the spinal fluid has been obtained. It must be recalled, however, that while the early syphilitic infection is general, there is a tendency for the spirochetal cause to localize itself in certain tissues, as in the aorta, but more especially in the central nervous system. When the central nervous system has been entered and changes in the tissues have resulted, as evidenced by a positive Wassermann reaction and cellular change in the spinal fluid, we have little to offer in the way of curative treatment and must be satisfied with the arrest of progress of the disease.

Contagion.—All cases of acute syphi-

[1] Stokes, J. H., and Brehmer, H. E.: Syphilis in Railroad Employees. THIS JOUR., 1919-1920, *1*, 419.

lis or those in which there are active lesions should be handled as contagious. In the later stages of the disease, as in locomotor ataxia and general paresis, there is little danger of contagion. These patients are suffering not so much from syphilis as from the destructive action of syphilis on the brain and the spinal cord.

FILE NO.	OCCUPATION	AGE	SOCIAL CONDITION	ORIGINAL DIAGNOSIS	WASSERMANN BLOOD	WASSERMANN SPINAL FLUID	FINAL DIAGNOSIS	DISABLEMENT COMPLETE	DISABLEMENT PARTIAL	TIME LOST DAYS	COST TO COMPANY	WORKING	HISTORY OF SYPHILIS
1183	CONDUCTOR	55	M	HEMIPLEGIA	POS	POS	ARTERIAL HYPERTENSION-SYPHILIS		✓	463	$983.75	NO	NO
1006	BLKSMITH	48	M	CHOREA	POS	POS	GENERAL PARESIS		✓	344	2100.00	NO	NO
1036	PEDESTRIAN	22	S	UNUNITED FRACTURE	POS		SYPHILIS				5500.00	NO	YES
1267	FIREMAN	31	W	UNCONSCIOUSNESS ACUTE	NEG	POS	CEREBRO-SPINAL SYPHILIS		✓	425	20.00	NO	YES
1599	ENG.	60	M	CHRONIC SYPHILIS	POS	NEG	" " "		✓	30		NO	YES
1050	ENG.	49	M	INFLUENZA	POS	NEG	" " "		✓	232	580.00	NO	NO
1177	WATCHMAN	42	M	UNCONSCIOUSNESS ACUTE	POS	POS	" " "		✓	2003	2445.00	NO	NO
1452	ENG.	46	M	DIAG. MENTAL CONDITION	POS	POS	" " "		✓	206	225.00	NO	NO
1094	BRKMAN	44	M	FOR DIAGNOSIS	POS	POS	" " "		✓	61	177.00	NO	YES
970	TEL OPR.	33	M	LOSS OF MEMORY	POS	POS	" " "		✓	365	17.50	NO	NO
1368	BLKSMITH	28	M	MENTAL CONDITION	POS	POS	" " "		✓	599	916.50	NO	YES
1403	BRKMAN	38	S	AMP. OF LEG DISABLED	POS	POS	" " "		✓	116	273.00	NO	NO
1424	LABORER	36	M	BURN OF LEG UNHEALED	POS		CHRONIC SYPHILIS		✓	75	42.50	NO	YES
1148	ENG.	43	M	TABES DORSALIS	POS		TABES DORSALIS	✓		1125	1796	NO	NO
1498	BRKMAN	48	S	AMP. OF LEG	POS	POS	GENERAL PARESIS		✓	762	773.50	NO	YES
1491	FIREMAN	37	M	COLITIS	POS		CHRONIC SYPHILIS		✓	114	243.00	NO	NO
1496	BRKMAN	51	M	TABES DORSALIS, ANEURISM	POS		TABES DORSALIS, ANEURISM	✓		1131	1480.50	NO	YES
58	COOK	48	M	RHEUMATISM	POS		ATAXIC PARAPLEGIA	✓		76	750	NO	NO
980	ENG.	44	M	TABES DORSALIS	POS		GENERAL PARESIS		✓	260	550.00	NO	NO
949	ENG.	50	M	SYPHILIS	POS		TABES DORSALIS		✓	97	374	NO	NO
636	CONDUCTOR	46	M	NEURASTHENIA	NEG	POS	GENERAL PARESIS	✓		502	2276.*	NO	NO
663	BRKMAN	39	M	OPTIC NEURITIS	NEG	POS	CEREBRO-SPINAL SYPHILIS	✓		1745	2294.50	NO	NO
723	FIREMAN	25	M	DIAGNOSIS	POS	POS	GENERAL PARESIS	✓		457	774	NO	YES
412	BRKMAN	32	M	INFLUENZA	POS		CHRONIC SYPHILIS	✓		76	195	NO	NO
813	FIREMAN	40	M	INJURY TO KNEE	POS		CHRONIC SYPHILIS		✓	149	505.00	NO	NO
1318	BRKMAN	37	M	UNUNITED FRACTURE	POS		CHRONIC SYPHILIS	✓		500	1749.25	NO	NO
268	MACHINIST			SACRO-ILIAC DISEASE	POS		SYPHILITIC OSTEITIS		✓	54	87.00	NO	NO
1425	BRKMAN			CONTUSION OF LEG	POS		SYPHILITIC PERIOSTITIS		✓	89	143.00	NO	NO
985	ENG.	39	M	CONTUSIONS-DELAYED RECOVERY	POS		CHRONIC SYPHILIS		✓	359	881.25	NO	NO
1550	LABORER	33	M	RHEUMATISM	POS	POS	CHRONIC SYPHILIS		✓	119	232.00	NO	YES
1128	BRKMAN	47	M	T.B. SINUS OF STERNUM	POS		GUMMA, CHRONIC SYPHILIS	✓		2003	2495	NO	NO
1356	HOSTLER	45	M	MYALGIA	POS		CHRONIC SYPHILIS		✓	82	225.00	NO	YES
850	BRKMAN	36	W	FRACTURE OF RIBS	POS		CHRONIC SYPHILIS		✓	71	108.50	NO	YES
931	LABORER	44	M	CONTUSION OF KNEE	POS		SYPHILITIC OSTEITIS		✓	591	473.00	NO	NO
1124	MACHINIST	38		INFLUENZA	POS		CHRONIC SYPHILIS		✓	75	42.50	NO	NO

COST TO CLAIM DEPT. $25,415.00
COST TO RELIEF DEPT. 25,296.10
TOTAL $ 50,711.10

TOTAL DAYS 13,946 — $ 25,296.10 — 12 POSITIVE, 23 NEGATIVE

FIG. 1.—Tabulation of findings in thirty-five cases of syphilis.

Are Syphilitics Safe as Trainmen?—All syphilitics should be considered potentially unsafe as workers until effective treatment has been instituted and their progress toward recovery carefully followed. It is my firm conviction that all syphilitics with an invasion of the central nervous system should be considered unsafe as trainmen and should not be permitted to operate trains until it is proved that they are cured. They are unsafe as trainmen because of the liability of sudden attacks of unconsciousness, of uncertain memory, of defective judgment and last, but by no means the least, because of the ideas of grandeur that characterize certain cerebrospinal cases.

The following extracts from case reports are cited by way of illustration.

CASE 1 (970).—A telegraph operator, aged 33, married, was reported for unsatisfactory service by the Division Superintendent, who

stated that he forgot to deliver mail and baggage and could not copy a Western Union message correctly. The superintendent was afraid that the man would fail to deliver a train order. A diagnosis of general paresis was made on the basis of positive blood and spinal fluid reactions.

CASE 2 (1094).—A brakeman, aged 44, married, was subject to hallucinations and peculiar spells. A diagnosis of cerebrospinal syphilis was made; the blood and spinal fluid were positive.

CASE 3 (1452).—An engineer, aged 46, married, was reported by a fellow-engineer because of his peculiar actions. The case was diagnosed as cerebrospinal syphilis; the blood and spinal fluid were positive.

CASE 4 (1267).—A fireman, aged 31, a widower, became suddenly unconscious in the cab of an engine and fell to the floor, where he remained for two hours. Upon his recovery he had no memory of the attack. A diagnosis of cerebrospinal syphilis was made; the blood was negative, the spinal fluid positive.

CASE 5.—J. S., a brakeman, aged 35, married, entered the hospital with the history of having fallen from a slowly moving train; the cause of his fall was unknown. He had a few superficial scratches. His conductor stated that he had reported him several times for inattention, forgetfulness, and general unsatisfactory service. He sent him to bring nine cars from a siding, and he brought out eighteen. When questioned, the brakeman said that he had only nine. He had a penile scar, and gave a history of infection in August, 1921. He had received no treatment. The blood reaction was 100 per cent. positive.

CASE 6.—An engineer ran past a signal set against him and a rear-end collision with another freight train resulted. The engineer and fireman were killed. A bottle of mercury tablets was found in the engineer's pocket, and investigation proved that he was being treated for syphilis.

While defective memory may lead to serious loss of life or property, it is not nearly so dangerous from the railroad point of view as the condition generally known as "idea of grandeur," where the person is convinced of his superior intellect and his freedom from the usual restraining customs and orders of his life and occupation. One engineer with syphilis (included in this series) had a boiler explosion; perhaps he reasoned that water in the boiler was necessary for other engineers but not for him. Another engineer with syphilis, with a previous good record, passed a danger signal, thereby wrecking two trains. Perhaps he thought that stop signals were all right for the average engineer but not for him. These examples show that all trainmen with syphilis are dangerous to themselves, to the public, and to the company; and all trainmen who are questioned about their failure to comply with rules having to do with the safety of trains should have a medical examination before they are permitted to resume their duties.

Syphilis at Time of Employment.—It was shown by Stokes and Brehmer that 26 per cent. of the patients with syphilis contracted the disease between the ages of 17 and 20 years; 32 per cent., between 20 and 25; and nearly 60 per cent. previous to 25 years of age. It must be concluded, therefore, that a large number were syphilitic at the time of employment. It is quite obvious that figures with regard to time of infection could not be obtained from industrial sources such as this series which I have reported, yet I feel that the experience of Stokes and Brehmer so accords with my own private experience that their figures can be accepted as applying to railroad men.

Can Syphilis Be Detected by Ordinary Physical Examination for Employment?—Except in very obvious cases detection of the disease is impossible. By a slight modification of the routine examination, however, the number of cases detected can be substantially increased.

In the cases where syphilis is acquired after employment we must depend on publicity propaganda to make the infected persons recognize the dangers of the disease, and to lead them to seek early treatment. I am sure that every man is interested in syphilis, and I am equally sure that those who have any reason to suspect the possibility of disease would seek information if they knew where to find it, and if they were certain that there would be no publicity.

In conclusion I would suggest that in routine examination more attention be paid to the genitalia for scars or other evidence of infection; to pupillary reactions; to absence or exaggeration of deep tendon reflexes; to the presence of pigmented scars over the shins, and to the Romberg test. All persons presenting deviation from normal should be carefully questioned and examined, and, if necessary, a Wassermann test should be made. I realize that there may be some objection to the additional expense entailed in making such examinations. Up to May 1, 1921, the thirty-five cases which I have reported have cost the company over $50,000 in money paid out, and how much more indirectly no one knows. We must not overlook the fact that at this stage these persons are, for the most part, beyond human aid and must necessarily go down to mental breakdown and death, and that nearly all of them could have been cured had their condition been recognized early. This number is but a small percentage of the cases of the disease prevailing in our service. Had we been able to prevent three or four of these thirty-five cases from going on to complete disablement, we would have saved enough money to cover the additional expense of the proposed examination.

I have purposely avoided mention of certain interesting problems, chief among which are those regarding treatment—namely, the sufficiency of treatment as given by the average medical man, and the provision of opportunity for the proper treatment of persons who are unable to pay. I hope that some solution of these problems may soon be offered.

THE PHARMACOLOGY OF SOME PHENYLENEDIAMINES*

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I. INTRODUCTION

OF the various phenylenediamines, the following are the most important for a study of their pharmacological actions and toxicity because of their extensive use in science, industry and the arts: meta-phenylenediamine, para-phenylenediamine, and the dimethyl and diethyl derivatives of the latter. They are used as reagents in the manufacture of dyes, in dyeing furs and pelts, and in the rubber industry, and they cause a peculiar, specific edema of the head and neck. The existing pharmacological studies are incomplete and contradictory, and deal principally with para-phenylenediamine. The dimethyl and diethyl derivatives of para-phenylenediamine have been scarcely studied at all. It seemed desirable, therefore, to repeat and extend the observations on these phenylenediamines. Ortho-phenylenediamine is too toxic for many purposes and has not been included in the present study. Before proceeding to the body of the paper, a review of the literature pertaining to the uses, toxicity, and pharmacological actions of the phenylenediamines will be presented.

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II. LITERATURE

Use as Reagents.—Formerly, para-phenylenediamine and its dimethyl derivative, which is more sensitive, were used by the older biologists (1) as reagents for the detection of ozone and peroxides in plant juices and animal cells. This use was based on a color change which these compounds undergo in the presence of oxygen (O_2), namely, from a light straw or no color to blue or violet. This change is rather sensitive, and on the strength of positive tests it was claimed that plant juices and saliva contained peroxides. Serum free from cells fails to give a positive reaction. A positive reaction is also unobtainable after treatment with hydrocyanic acid. Presumably, the intra-

cellular enzymes (oxidases) are at least in part concerned in this reaction, although the exact mechanism of action has not been definitely ascertained. According to Battelli and Stern (2), blood and all tissues of higher animals possess strong oxidizing powers for para-phenylenediamine; the oxidizing power of the brain, heart, muscles, kidneys, and liver is very intense, while that of the pancreas, spleen, and lungs is very weak. It is claimed by these investigators that the white substance of the brain is more active than the gray substance. The power of oxidation of these compounds possessed by the tissues of many animals is not altogether lost by boiling and by the addition of mineral acids.

In another study on various factors which influence the oxidation process, Battelli and Stern (3) conclude that the oxidation of para-phenylenediamine by animal tissues takes place most energetically in the presence of water, and that the addition of or treatment with acid, alkali, concentrated salt solutions, acetone, and alcohol, retards or inhibits the reaction. Muscle heated to 60°C. is no longer able to oxidize the para compound. Dimethyl-para-phenylenediamine, together with *a*-naphthol, is used as a reagent by histologists to demonstrate the presence of oxidase granules in cells (4). The responses with different cells are so variable, however, that the quantitative feature of the reaction appears doubtful, the differences being presumably due to differences in permeability of cells and carelessness in the handling of specimens in the presence of atmospheric oxygen, which suffices to produce the oxidative change.

Besides their use as reagents, the phenylenediamines are used chemically for the manufacture of indicators and dyes, such as chrysoidine, Bismarck brown, and methylene blue (5).

Poisoning from Hair and Fur Dyes.—Under the name of ursol, para-phenylenediamine is used extensively for the dyeing of furs and pelts. It is also a common constituent of certain hair dyes, and many cases of poisoning from such hair dyes are reported in the literature (6). The other important constituent of this class of hair dyes is iron which, when mixed with para-phenylenediamine, gives a black color. Recently, Thompson (7) observed the following symptoms after the use of the French hair dye, "goute à goute," which contains para-phenylenediamine: vertigo, gastritis, diplopia, asthenia, and exfoliative dermatitis. Knowles (8) reports similar symptoms, including dermatitis, from cosmetics and wearing apparel (furs, stockings, etc.) containing para-phenylenediamine. These reports agree with reports of the older observers, which may be found in works on toxicology by Kunkel, Kobert, and Brouardel (6), and need not be detailed here. In Germany, according to Gerdon (9), para-phenylenediamine, because of its toxicity, is being replaced in cosmetics by the non-toxic aureol.

The commonest afflictions observed among fur and hide workers exposed to dyes containing para-phenylenediamine are asthma and eczema. The cause of the asthma has given rise to considerable speculation. Gerdon (9) and Curschmann (10) attribute the asthma to an anaphylactic reaction. The attacks occur chiefly during the stage of drying the dyed pelts and at a time when they are treated with sand and pulled out of dye containers. These manipulations are accompanied by clouds of dust containing para-phenylenediamine and

its oxidation products, which the workers inhale. Curschmann claims that fur-dye workers become hypersensitive, and become ill even when handling the finished products (dyed furs). Both Gerdon and Curschmann claim that guinea-pigs, which have been injected with serums of individuals suffering from ursol poisoning, respond with severe anaphylactic symptoms when they are reinjected intravenously and hypodermically with the oxidation product, quinonediimine, and also when they inhale it. Their evidences are not convincing, however, since it is now known that numerous foreign substances of diverse nature can cause anaphylactoid symptoms, but not true anaphylactic shock. On the contrary, it appears more probable that the responses in human individuals and in guinea-pigs occur directly and as a result of the marked irritant properties of para-phenylenediamine. This is the view of Sartory and Rousseau (11), and is supported by the results of my experiments. On the basis of animal experiments, Sartory and Rousseau state that the oxidation product, quinonediimine, is pharmacologically inert and is not responsible for the irritant effects of hair and fur dyes containing para-phenylenediamine. In support of the claim that ursol exerts a direct irritant effect on the respiratory passages, the presence of pharyngitis and laryngitis reported by Ritter (12) may be cited. The eczematous appearance of the skin can be explained as being due to a dermatitis resulting from direct irritation by the dye in the same way as dermatitis of the scalp occurs from the use of hair dyes discussed above.

Use in Rubber Industry.—The extensive use of various amino compounds, including aniline and the phenylenediamines, as accelerators in the vulcanization of rubber has been known for some time (13) (14) (15). The following phenylenediamines are reported as being used for this purpose: meta-phenylenediamine, para-phenylenediamine, and dimethyl-para-phenylenediamine (16). Poisoning from the use of aniline in the rubber and other industries is well known (17); from our knowledge of poisoning from hair dyes and in the fur industry, the same result might be expected from the use of the phenylenediamines in the rubber industry. It does not follow from this, however, that the finished rubber product is toxic or injurious as a result of the use of such accelerators, since it is claimed that these compounds are destroyed during the process of vulcanization. On the other hand, the formation of new products just as toxic, or even more toxic, from the contact of rubber and such aniline-like accelerators is possible.

It is stated in the Bulletin of the Bureau of Labor Statistics for 1915 (17) that certain aniline-like compounds, when heated with rubber, form guanidine, a strong muscle-nerve poison which causes increased irritability, convulsions, and other symptoms. Similar symptoms have been recently reported by Stokes and Busman (18) and Busman (19) from the use of gum-rubber tubing in the intravenous injection of arsphenamine and other compounds. Whether the reactions described by Stokes and his associates are due to the presence of the aniline type of accelerator, or to guanidine-like products, is not known. According to some manufacturers, the rubber tubing intended for surgical purposes is not vulcanized with the aid of the aniline and phenylenediamine type of accelerators, but instead of these, hexamethyleneamine is used.

Nevertheless, it is known that accelerators are used extensively, and if any one of the phenylenediamines is used in the vulcanization of surgical rubber tubing, it is potentially toxic and its use is reprehensible. It will be shown by the results of my work that the phenylenediamines are distinctly toxic in very small quantities and concentrations.

Aside from the acute toxicities, the phenylenediamines and products of manufacture requiring their use may conceivably give rise to chronic effects, such as chronic pulmonary and skin diseases, nephritis, and tumor formation. Nassauer (20) reported the occurrence of cancer of the bladder among workmen in the organic chemical industry in which aniline and aniline-like compounds are used. Workmen may be employed for sixteen years before symptoms of the disease appear. On the other hand, tumors were not noted by Nassauer in men exposed to aniline-free benzene for twenty years. It is, therefore, of considerable interest and importance to ascertain the action and toxicity of such compounds as the phenylenediamines, which are chemically closely related to aniline.

Pharmacology.—As far as I can ascertain, the physiological effects of the phenylenediamines were first studied by Dubois and Vignon in 1888 (21). Their immediate interest in these compounds was their chemical resemblance to leukomains and ptomains. Although Dubois and Vignon reported results with the para and meta compounds, there is some doubt about the identity of their para compound, since it was obtained from ortho-nitraniline, which yields ortho-phenylenediamine. There is probably no question about the identity of their meta-phenylenediamine. The symptoms produced in dogs by the injection of 0.1 gm. per kilo of the para(?) compound consisted of salivation, vomiting, diarrhea, diuresis, marked exophthalmos, coma, and death within two or three hours. The injection of 0.1 gm. per kilo of meta-phenylenediamine in dogs caused symptoms resembling those of influenza—namely, continuous sneezing, hoarse cough due to marked irritation of the pharynx and the glottis, marked coryza, increased secretion of mucus and urine, and finally coma and death. At autopsy the lungs and abdominal viscera were markedly congested.

The symptoms of respiratory distress and congestion of viscera observed by Dubois and Vignon were subsequently confirmed by Erdmann and Vahlen (22) by experiments on rabbits and dogs. In addition, Erdmann and Vahlen showed that the administration of para-phenylenediamine to rabbits caused a peculiar specific edema of the head and neck, with marked swelling of the tongue, while the eyelids and tissues of the orbits gave the appearance of exophthalmos. They ascribed the edemas to the irritant action of the oxidation product, quinonediimine. According to these authors, the para-phenylenediamine circulated through the body, was excreted on the surfaces of membranes, and there in the presence of atmospheric oxygen was converted to quinonediimine, which in turn caused irritation and, consequently, edema. This hypothesis, as well as certain results of Erdmann and Vahlen with quinonediimine, was not supported by the totally negative results of Sartory and Rousseau (23) with the oxidation products of para-phenylenediamine in dogs, while the unoxidized compound was definitely toxic.

The edema observed by Meissner (24) was characterized by considerable maceration, with increased viscosity and fibrin content of the blood. Neither section of peripheral nerves with degeneration of the sympathetic fibers nor the administration of reducing agents or of preparations of glands of internal secretion influenced the edema, but the administration of 10 per cent. calcium chloride inhibited it, and atropine completely prevented death and edema of the tongue and head. Meissner concluded, therefore, that the mechanism of action was peripheral and presumably located in the muscles themselves. The blood pressure in rabbits remained unchanged, but the respiration increased during the edema. The dose of para-phenylenediamine by mouth necessary for the edema action was 0.4 gm. per kilo. In frogs three stages of action were observed by Meissner. In the beginning, the action was characterized by a narcotic-like paralysis. Later, convulsions of medullary origin occurred; finally permanent muscular stiffness occurred; and at death the animals appeared in rigor. The isolated heart was not markedly influenced by para-phenylenediamine, while the blood vessels in excised organs were constricted.

In a recent study on the comparative toxicity of several different phenylenediamines and their derivatives, Meissner (25) found that meta-phenylenediamine and dimethyl-para-phenylenediamine did not cause edema in rabbits, and that the ortho compound did so only in cats. Diethyl-para-phenylenediamine produced facial and neck edema in rabbits as readily as para-phenylenediamine. Dimethyl-para-phenylenediamine was fatal in very small dosage, and also caused hemorrhagic nephritis in rabbits.

In their experiments with meta-phenylenediamine on two rabbits and one rat, Hess and Müller (26) observed hydrothorax and fluid in the peritoneum, but they do not mention edema in the rabbits. The rat showed facial edema at the end of ten hours. The same effects occurred after the administration of toluylenediamine in dogs and rabbits—effects which Hess and Müller ascribed to increased filtration due to increased permeability of the capillaries produced by these compounds as indicated by the increase in concentration of the blood.

Whatever the true explanation of the peculiar edema may be, the results of my experiments indicate that it is a variable phenomenon. It is most readily induced in rabbits, less readily in cats, and thus far never in rats and guinea-pigs. The dosage necessary for the production of the edema, the character of the onset, and the time of appearance of the edema are also variable. These points will be discussed later in the paper.

According to Erdmann and Vahlen, the dark color of the blood after the injection of para-phenylenediamine in animals is not due to methemoglobin. These investigators claim that there is also a high increase in the ammonia content of the blood.

In man, the effects produced by para-phenylenediamine are analogous to those produced in animals, the symptoms consisting of asthma, eczema, chemosis, gastric irritation, lachrymation, and exophthalmos. By some investigators (S. Fränkel (27), and Erdmann and Vahlen (22)) these effects are attributed to irritation by the oxidation product, quinonediimine. Pollak (28) thinks that the effects are due to para-phenylenediamine. Others (v. Criegern (29), Gerdon (9), Curschmann (10), and

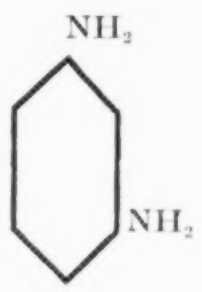
Doerr (30)) attribute the reaction to a true anaphylaxis. The reasons for believing that the anaphylactic view is untenable have already been stated and need not be discussed here. The evidences as to whether quinonediimine or para-phenylenediamine is responsible are conflicting. The literature contains no data regarding the actions of the dimethyl and diethyl derivatives upon man.

Medicinal Uses.—Meta-phenylenediamine was introduced into medicine, under the name of lentin, as an antidysenteric remedy by the chemist, Reidemeister (see Unverricht, 31), on the now obsolete theory that Asiatic cholera was a nitrite poisoning owing to the nitrite producing property of cholera bacilli in the intestine. According to this view, meta-phenylenediamine would bind the nitrite with which it combines readily. Favorable results from its use in diarrheas of different origin were reported by Unverricht (31) and Boye (32). Unverricht and Boye observed a brown coloration of the urine of children after doses of 0.01 to 0.02 gm. of meta-phenylenediamine; and of the urine of adults after doses of 0.1 gm. three times daily. It is claimed that constipative and astringent actions occurred after doses of 0.1 gm. administered to children. On the other hand, in animals, diarrhea occurred—a result which might be expected considering the irritant action of the agent. Since Boye limited the diet at the same time, it is very doubtful how much, if any, of the anti-diarrheal action was due to meta-phenylenediamine *per se*.

This review of the literature indicates the unsatisfactory state of our knowledge regarding the phenylenediamines. In view of their scientific importance and extensive use in certain industries, it is obvious that more definite knowledge of their toxicity and their actions is desirable. The following report deals with a description of the compounds used, their comparative toxicity, and local and systemic effects, together with a brief discussion of the practical application of the results.

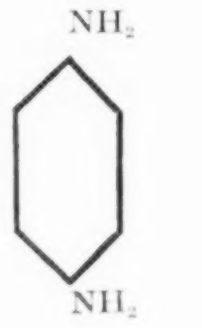
III. Description and Solubility of Compounds Studied

Meta-Phenylenediamine (Lentin).—The structural formula for this compound is



It is a pinkish crystalline solid with a melting point of 83° C.; it is almost tasteless and odorless, and gives from a deep reddish to a brownish color with sodium nitrite, and a yellowish color with ferric chloride.

Para-Phenylenediamine.—The structural formula of this compound is

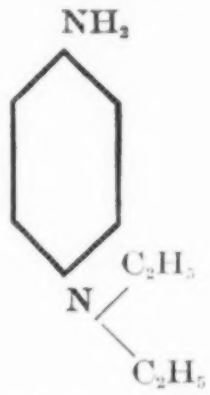


It is a dark brown, or nearly black, crystalline solid with a melting point of 140° C.; it possesses a slight burning taste and odor. With sodium nitrite it gives a wine-red color, and with ferric chloride first a yellowish, then a greenish to a brownish-black color.

Dimethyl-Para-Phenylenediamine.—The structural formula for this compound is

When freshly prepared it is a nearly colorless or light yellowish liquid with a strong, pungent odor suggestive of garlic, and very irritating. It possesses a burning, disagreeable taste. The melting point of fresh crystals is 40° C.; the boiling point of the liquid is 262° C. After standing for a few hours, it becomes black and tarry, and gradually deposits black crystals. It gives a dark greenish (nearly black) color with sodium nitrite, and a reddish color with ferric chloride. In the presence of ferric chloride and hydrogen sulphide it forms methylene blue.

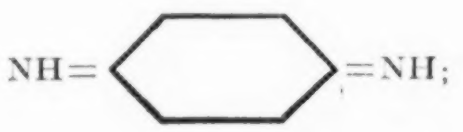
Diethyl - Para - Phenylenediamine. — The structural formula of this compound is



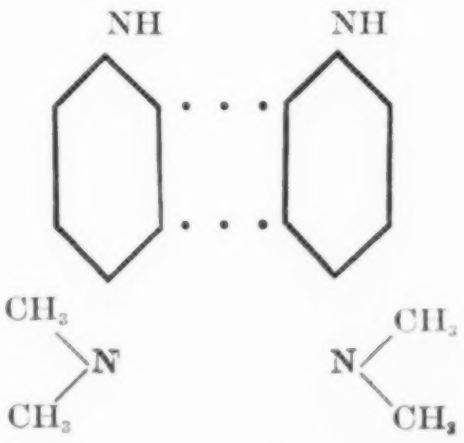
It is very unstable at ordinary room temperature, but more stable when dissolved in benzene. In this form and in its natural state it is a black, tarry liquid with a pungent odor which is less intense and less disagreeable than that of the dimethyl compound; its boiling point is 260° C. It gives a reddish color with ferric chloride.

The behavior of the different phenylenediamines toward different solvents was ascertained by adding 0.1 gm. or 0.1 c.c. of each compound to 10 c.c. of the solvent. The different compounds behaved in about the same way and may be described together. The bases themselves are only slightly soluble in water, but freely soluble in such lipoid solvents as 95 per cent. alcohol, cotton-seed oil, ether, and turpentine. They are practically insoluble (forming precipitates) in gasoline, kerosene, liquid petrolatum, and glycerine. The reaction of the watery solutions is alkaline. When treated with acids (hydrochloric and acetic), all of the bases form salts, which are readily soluble in water and possess an acid reaction. The aqueous solutions of the basic compounds are colored slightly pink to orange-yellow with meta-phenylenediamine, brown with para-phenylenediamine, and purplish-red or violet with the diethyl and dimethyl derivatives of para-phenylenediamine. The addition of acid intensifies and brightens the colors. On the other hand, the lipoid solutions possess a yellowish to brownish-black color.

The color of the aqueous solutions is due to the presence of the oxidation product, quinonediimine, which is formed immediately on exposure of the bases to atmospheric oxygen. The structural formula of the quinonediimine derived from para-phenylenediamine is



that from the dimethyl derivative is said to possess the following formula



It occurs as a dark polymerization product, a corresponding product being also obtained from the diethyl derivative.

The results with the different solvents indicate that the bases, being lipoid soluble, might be readily absorbed from the skin and cause local irritation, while the salts would be practically non-irritant and non-absorbable. This was found to be the case. Furthermore, it is indicated that alcohol and cotton-seed oil might be useful for the removal of these compounds from the skin, in the treatment of irritation, etc. Gasoline, kerosene, petrolatum, and glycerine, on the other hand, would be ineffective.

IV. Pharmacological Actions

1. *Fatal Dosage and Comparative Toxicity*

The minimal fatal doses of the different phenylenediamines were determined for rabbits, white rats, guinea-pigs, cats, and dogs. The compounds were used in the form of bases and salts, with and without solvents, depending upon the method of administration. The hypodermic, intravenous, and gastric administrations were made with aqueous solutions of different strengths. For gastric administrations a stomach tube was used, and the dose was washed down with a little water in order to remove the last traces of the solution. The methods used for studying dermal and vapor toxicities will be described separately. The results that were obtained are presented in Table 1.

Para-Phenylenediamine. — When administered subcutaneously, the minimal fatal dose of para-phenylenediamine for white rats was found to be 0.17 gm., and for rabbits 0.2 gm. per kilo. On the other hand, the fatal dose by stomach for a cat was less than one-half that for rabbits—namely, 0.1 gm. per kilo. The fatal dosage by intravenous administration was found to be rather variable in the few dogs that were used. Further sacrifice of animals in order to determine the fatal dosage by intravenous injection of this and other compounds was deemed unwarranted. The definitely effective dose of para-phenylenediamine administered intravenously was about 0.017 gm. per kilo.

Dimethyl-Para-Phenylenediamine. — The minimal fatal dose by hypodermic administration for white rats was 0.05 gm., for rabbits 0.06 gm., and for guinea-pigs 0.1 gm. per kilo. Gastric administration to rabbits required 0.15 gm. per kilo to cause death, and one cat required only 0.02 gm. per kilo.

These results are in accord with the findings in regard to para-phenylenediamine—namely, that cats are more susceptible to these poisons than are rodents.

Intravenously administered, the minimal fatal dose for dogs was about 0.051 gm. per kilo, the lowest effective dose being about 0.003 gm. per kilo. The results with the different species are variable, but, on the whole, they indicate that para-phenylenediamine is much less toxic (roughly one-third to one-half) than its dimethyl derivative.

Diethyl-Para-Phenylenediamine.—As indicated by the results in Table 1, this compound appears to be of about the same toxicity as para-phenylenediamine, but it is decidedly less toxic than the dimethyl derivative. The minimal fatal dose by hypodermic administration for white rats was 0.1 gm., for rabbits 0.25 gm., and for guinea-pigs 0.2 gm. per kilo. When administered intragastrically to rabbits, the fatal dose was 0.45 gm. per kilo, and in one cat 0.3 gm. per kilo. These results again indicate the greater susceptibility of cats than of rodents to these poisons. Administered intravenously, the mini-

mal fatal dose for dogs was 0.07 gm. per kilo — a larger dose than was required of dimethyl-para-phenylenediamine (0.051 gm. per kilo). The results indicate considerable variability in the response of different species, white rats, on the whole, being the most susceptible, cats and rabbits next in order, and guinea-pigs the least susceptible.

Meta-Phenylenediamine. — The minimal fatal dose for white rats, when administered hypodermically, was 0.08 gm., and for rabbits 0.2 gm. per kilo. According to these results, the meta compound is once again as toxic as the para compound for white rats, and about equally as toxic as the para compound for rabbits. On the other hand, the results with gastric administration indicate that the meta compound is less toxic than the para compound. That is, rabbits required 0.3 gm., and each of two cats also required 0.3 gm. per kilo to cause death. These results agree with those of previous investigators using the same method, and tend to demonstrate that meta-phenylenediamine is less toxic than para-phenylenediamine. When administered intravenously to dogs, the definitely effective dose for the circulation was 0.017 gm. per kilo, the lowest effective dose observed being 0.006 gm. per kilo.

Toxicity from Skin.—This was determined by direct application of definite quantities of the different compounds themselves (in basic form) to the shaved skin of rabbits. Twenty-five square centimeters of skin were used and a single application was made on each animal. After the skin had been shaved, it was washed with water in order to remove the excess of soap, and the application was made to an uninjured area. The animals were fastened to boards until symptoms developed; then they were untied and removed to cages for further observation. Meta-phenylenediamine and para-phenylenediamine were used in dry form and in strong alcoholic solution. The effects of the strongest (10 per cent.) alcoholic solutions were not fatal, consisting only of moderate erythema. These compounds can, therefore, be regarded as practically non-toxic when applied locally, except for the mild dermatitis which they produce. The result might be quite different with repeated applications upon the same area — as, for instance, in chronic intoxication from hair dyes and in the dyeing of furs—or when applied to injured skin. The unlimited possibilities of producing intoxications of this kind were not feasible for testing under the conditions of the investigation.

On the other hand, the dimethyl and diethyl derivatives of para-phenylenediamine were decidedly toxic, causing death from the application of very small quantities in from fifty minutes to three hours. Definite quantities of the compounds measured with a pipette graduated to 0.005 c.c. were spread evenly over 25 sq. cm. of the shaved and uncovered skin in the same way as were the meta and para compounds. The local and systemic effects will be described later. With dimethyl-para-phenylenediamine the minimal fatal dose was 0.0024 c.c., and with diethyl-para-phenylenediamine, 0.005 c.c. per square centimeter per kilo of body-weight, indicating that the diethyl compound is only about half as toxic as the dimethyl compound. Dogs were found to be less suitable for experiments of this sort. The fatal doses of the two compounds for rabbits were applied in the same way on two dogs. Both compounds caused considerable erythema and urticarial rash; in addition, the dimethyl compound caused

marked swelling of the skin. The animal receiving the dimethyl compound (0.84 c.c. on 200 sq. cm. of skin) was found dead the following morning (at the end of twenty hours). Assuming that the skin absorption in man and rabbits is about the same, the fatal dose for an adult of 60 kilos body-weight would be about 3.6 c.c. for 25 sq. cm. of skin area, or the equivalent of about one teaspoonful of dimethyl-para-phenylenediamine on the palm of the hand. With the exception of acetylcholin, there are no other poisons, as far as I know, which, when applied to the unbroken surface of an organ (mucosae and serous surfaces are not referred to here), cause typical symptoms of systemic poisoning like the dimethyl and diethyl derivatives of para-phenylenediamine. In this sense, these phenylenediamines may be regarded as unique and very efficient poisons, since they cause symptoms and even death from application to unbroken skin. Acetylcholin was found by Hunt (33) to cause a fall of blood pressure when applied to more favorable locations—namely, the surfaces of trachea, liver, and skeletal muscles.

TABLE 1.—MINIMAL FATAL DOSES OF SOME PHENYLENEDIAMINES[1]

Animal	Para-Phenylene-diamine	Diethyl-Para-Phenyl-enediamine	Dimethyl-Para-Phenylenediamine	Meta-Phenyl-enediamine
		Subcutaneously		
White rat	0.17 (10)	0.10 (15)	0.05 (14)	0.08 (11)
Rabbit	0.20 (3)	0.25 (12)	0.06 (12)	0.20 (2)
Guinea-pig		0.20 (9)	0.1 (3)	
		Intragastrically		
Rabbit	0.25 (7)	0.45 (6)	0.15 (4)	0.3 (4)
Cat	0.10 (1)	0.30 (1)	0.02 (1)	0.3 (2)
		Intravenously		
Dog	0.017 gm. (3) definitely effective	0.07 (3) just effective= 0.005 per kg.	0.051 (8) just effective= 0.003 per kg.	0.017 (3) definitely effective
		Vapor		
White rat	none	no effects (5)	1:500,000 survived (5)	– –
Guinea-pig	none	no effects (3)	1:7,000,000 1:5,000,000 (3) 1:4,200,000	– –
Rabbit	none	no effects (1)	1:2,000,000 (1)	– –
		From Skin		
Rabbit	none (3)	0.005 c.c. per sq. cm. per kilo (10)	0.0024 c.c. per sq. cm. per kilo (13)	none (3)
Dog	– –	0.004 c.c. per sq. cm. per kilo not fatal (1)	0.004 c.c. per sq. cm. per kilo (1)	– –

[1] Figures outside of parentheses represent grams per kilo; those within parentheses, number of animals used.

Vapor Toxicity.—This is of interest in connection with the industrial uses of phenylenediamines, especially of dimethyl-para-phenylenediamine which is rather volatile. Preliminary trials with the dimethyl and diethyl derivatives of para-phenylenediamine indicated that the saturated vapors of the dimethyl derivative were distinctly toxic, being fatal to white rats under a bell-jar. The vapors of the diethyl derivative produced no symptoms whatever. The para and meta compounds are non-volatile at ordinary room temperature and at 38° C. The quantitative study of vapor toxicity was limited, therefore, to dimethyl-para-phenylenediamine. The method used was practically the same as that used for the study of irritant war "gases" previously described (34).

The animals were placed in a 5-liter, wide-mouthed bottle lying on its side and having an inlet and outlet for the toxic vapors. The inlet was connected by glass and rubber tubing to a bubbler containing the compound and immersed in a water bath at constant temperature. The bubbler, in turn, was joined to a flow-meter through which air was blown by means of an ordinary motor and blower. By varying the temperature around the bubbler and the volume of air passing through it, it was possible to vary the concentration of vapors of the compound. The nominal vapor concentration of the compound to which the animal was exposed was obtained by dividing the loss of weight of the bubbler by the volume of air which passed through it. A verification of the nominal vapor concentration by chemical analysis was not deemed necessary for my purposes. The figures which follow refer to nominal concentrations only.

Considerable variation in the response of different species to the vapors was found, and this is in general agreement with the variations in toxicity observed after gastric and subcutaneous administration of the compound. White rats just survived concentrations of 1:500,000; higher concentrations were fatal. Rabbits required much lower concentrations (1:2,000,000) and guinea-pigs were killed by still lower concentrations (1:7,000,000 to 1:4,200,000). The symptoms consisted of restlessness, dyspnea, convulsions, and death. The animals wiped their nostrils and licked their chops, thus indicating local irritation by the poison, but no increase in salivation or frothy fluid indicative of pulmonary edema was evident. The symptoms presumably occurred as a result of alveolar absorption of the compound itself, and were identical with those from other methods of administration.

Comparative Toxicity.—Owing to the marked variations that were encountered in different species and sometimes in the same species, an accurate comparison, according to the minimal fatal dosage of the different compounds, is difficult. In connection with the discussion of the toxicity of the individual compounds, comparisons were made in this way in a few instances. These comparisons and the results given in Table 1 indicate that dimethyl-para-phenylenediamine is the most toxic of all the compounds studied. This is true when it is administered hypodermically, gastrically, dermally, and through the lungs. It is, roughly speaking, about two to three times as toxic as diethyl-para-phenylenediamine and para-phenylenediamine when administered hypodermically and gastrically. Diethyl-para-phenylenediamine appears to be no more toxic than para-phenylenediamine, and meta-phenylenediamine does not differ markedly in its toxicity from the para compound, being only

slightly less toxic when administered gastrically, and somewhat more toxic for rats when injected hypodermically. None of these compounds produced fatal effects when applied to the skin, and diethyl-para-phenylenediamine was not toxic in vapor form. There is no question, therefore, that dimethyl-para-phenylenediamine is the most toxic of the compounds that were studied. This marked toxicity is due in part to its volatility and lipoid solubility, and in part to the methyl groups which it contains.

Accurate comparisons with the results of previous investigators are impossible because the objects of their experiments were different and their results were also variable. Their experiments were usually aimed at the reproduction of symptoms observed in human individuals from the use of hair dyes or exposure to dyes in the fur industry, and at the reproduction of edema in animals. For instance, the results of Meissner indicate that 0.074 gm. per kilo of para-phenylenediamine was fatal to a cat; that 0.082 gm. per kilo of the diethyl derivative was not fatal. The results of Erdmann and Vahlen are similarly irregular. These authors used from 0.04 to 0.4 gm. per kilo of the para compound to produce edema in rabbits, and it is not recorded whether the administrations were fatal. In dogs, hypodermic administration of 0.022 gm. per kilo caused marked symptoms, intravenous administration of 0.033 gm. per kilo gave no effects, and gastric administration of 0.05 gm. per kilo caused very marked symptoms. Obviously the fatal dosage and limits of toxicity cannot be accurately determined in this way. The results presented in this section give, therefore, a more definite idea of the toxicity of the phenylenediamines than was previously obtainable.

2. *Local Effects*

A study was made of the effects of the different phenylenediamines on the skin of rabbits and on human skin. The skin was previously shaved, washed with soap and water, and dried. The compounds were then applied directly to the uninjured areas of about 25 sq. cm. of rabbit's skin, and of 1 to 5 sq. cm. of human skin. The skins were left uncovered. The animals were tied to boards for varying periods of time during the observation of the acute effects, and were observed daily thereafter in their cages until the lesions disappeared. When symptoms of systemic toxicity appeared, the animals were untied and replaced in their cages.

The application of meta-phenylenediamine and para-phenylenediamine in dry basic form rubbed into the skin had no effect. Ten per cent. alcoholic solutions of these compounds produced only a mild erythema on rabbit's skin, and a slight burning and itching sensation on human skin. In some individuals no effects whatsoever could be demonstrated. Different results might be obtained with continued applications over long periods of time, as in chronic poisoning, or with applications on injured skin. Sand-papered areas or injuries on rabbit's skin from shaving responded with more redness and more pronounced urticaria, but no blisters, nor lasting effects were produced. There were also no demonstrable symptoms of systemic toxicity with the meta and para compounds when applied in this way. It was concluded, therefore, that these compounds are relatively non-toxic and non-irritant for rabbit's skin. This is

probably also true for human skin, as far as acute dermatitis and toxicity are concerned. There were no prospects of securing adequate material for proper study of chronic poisoning, however, and further study with these compounds was, therefore, abandoned.

On the other hand, the dimethyl and diethyl derivatives of para-phenylenediamine were found to be very irritating and toxic when applied to healthy skin. The effects of these two compounds differed quantitatively, but were the same qualitatively. They may, therefore, be described together.

Rabbit's Skin.—Dimethyl-para-phenylenediamine in different quantities, ranging from 0.0001 c.c. to 0.0062 c.c. per square centimeter of skin per kilo of body-weight, was applied to the skins of twelve rabbits, and diethyl-para-phenylenediamine in quantities ranging from 0.0018 c.c. to 0.006 c.c. per square centimeter of skin per kilo was applied to the skins of ten rabbits. The results were uniform throughout, being more pronounced with the higher than with the smaller quantities. The following protocol will give some idea of the results that were obtained.

PROTOCOL.—Rabbit. 2.3 kg.

Before Experiment. — Respiration, 60; pulse, 200; temperature, 39° C.

2:10.—0.2 c.c. of dimethyl-para-phenylenediamine applied to 25 sq. cm. of skin.

2:15.—Struggling.

2:18.—Beginning wheal formation; skin raised. Occasionally struggling.

2:25.—Marked tremor followed by convulsions, chiefly in the extremities; pupils dilated. Respiration, 246; pulse, 228. Mucosae, cyanotic; tongue, blue.

2:33.—Marked, continuous bilateral convulsions throughout the body; cyanosis; pupils dilated; loud wheezing. Marked wheal covering entire area of application. Respiration, 198.

2:40.—Marked frothing of saliva; pupils widely dilated; wheezing; convulsions. Pulse full and slow, 120; temperature, 39.8° C.

3:14.—Animal lying on side; died while pulse was being taken. Pulse, 180; temperature, 38.5° C. Respiration stopped before heart. Marked cyanosis; pupils dilated.

Autopsy. — The only important changes noted were: discoloration of the skin at the site of application of poison; underlying tissue very gelatinous; some discoloration of fascia and muscle underneath. The blood was very dark, with a tinge of brown. Spectroscopic examination showed the presence of reducible oxyhemoglobin by ammonium sulphide ($(NH_4)_2S$). Marked cyanosis of all viscera.

Both compounds caused marked discoloration of the skin and underlying tissues, the areas appearing from a light blue to black according to the quantity of the compound used. In from fifteen to thirty minutes there was considerable rash and wheal formation with spreading swelling, the painted area being sharply raised above the surrounding skin. At the end of two to three hours, the entire area to which the compounds were applied was uniformly swollen, prominent, pouchy, and soft, rising to a height of 2 to 3 cm. The swellings were movable and appeared to be limited to the skin. There was no coagulation or erosion of tissue. The local swellings persisted for variable lengths of time in different animals, and did not seem to be altogether dependent upon the dosage, although the larger quantities tended to produce more pronounced and more lasting swellings. As the highest doses killed the animals, the relation of the dosage to the degree of effect was difficult to establish. With some animals the lesions remained several weeks (from four to six); with others, from twelve to fourteen days. As a rule, the skins healed completely, leaving only a dried, dark area at the site of application, and this eventually desquamated. There were no infections and suppurations.

The systemic symptoms which accom-

panied the local effects were rather marked. After the initial symptoms of local irritation, the animals remained quiet for about ten to fifteen minutes. Then the respiration and the pulse gradually became accelerated; there were increased reflex excitability, marked struggling, cyanosis, and, finally, convulsions of the medullary and spinal types. With the smaller doses of the dimethyl derivative (about 0.001 c.c. per square centimeter per kilo) increased reflex excitability and only one or two convulsions occurred, but with the higher doses (0.005 to 0.006 c.c. per square centimeter per kilo) the convulsions were continuous, and death occurred in from fifty minutes to two hours after the application of the agent. These symptoms were similar to those following hypodermic administration of both derivatives, and were due to the agents themselves. At autopsy the only important changes observed consisted of marked cyanosis of all viscera; rather pronounced intestinal peristalsis, and a marked discoloration at the site of application, extending through the subcutaneous fat to the aponeurosis of the recti muscles. The skin at the site of application was markedly edematous, being very gelatinous, soft, and macerated. As a rule there was very little surface extension of the dark discoloration beyond the area of application. The blood of some animals appeared brownish, and that of others was very dark. Definite proof of the existence of methemoglobin by the usual spectroscopic tests was not obtained, however. The dark color of the blood was complicated by the presence of the compounds themselves, which become nearly black on contact with tissues. It was difficult, therefore, to ascertain how much of the dark color of the cyanotic blood was the result of ordinary asphyxia, and how much was due to the compound. In dogs injected with these compounds and receiving artificial respiration, the blood also remained very dark.

Human Skin.—The effects of dimethyl-para-phenylenediamine and diethyl-para-phenylenediamine were observed on six subjects. The quantities of the dimethyl derivative used ranged from 0.001 c.c. to 0.005 c.c. per square centimeter of skin; the quantities of the diethyl derivative, from 0.005 c.c. to 0.02 c.c. The effects were more pronounced with the larger quantities.

The effects following the application of dimethyl-para-phenylenediamine consisted of local heat, tenderness, erythema, maculopapular rash with quantities of 0.001 c.c., and blisters with the larger quantities. The effects appeared in from fifteen to thirty minutes, and spread to about six times the original area of application. Itching at this time was rather marked. On the second or third day there were hemorrhages and changes in blood pigment in the deeper layers of the skin. From the third day on, the lesions were quiescent and seemed to be healing; they appeared completely healed about the eighth day. On the eighth day, however, three subjects experienced marked itching, and gradually there appeared wheals with considerable erythema in the same areas to which the compounds had been originally applied. These symptoms persisted for about two weeks, and then gradually disappeared without causing further annoyance.

The same six subjects responded with temporary local heat and marked itching and two of them showed also a papular rash after the application of about five times the quantity of diethyl-para-phenylenediamine. These effects indicate that the diethyl derivative is less

irritating than the dimethyl derivative. There were no blisters and no late effects, all signs and symptoms of irritation being absent on the following day.

The application to human skin of both the dimethyl and diethyl derivatives in the form of salts (hydrochlorides) in solution produced no effects at all. In this form the compounds are not lipoid soluble, and are therefore not absorbed from the skin.

The effects on the skin caused by these compounds in vapor form are practically negligible. The jacketed test-tube method of Lynch, Smith and Marshall was used in these experiments. Exposures of skin to saturated vapors of dimethyl-para-phenylenediamine for thirty minutes caused only small papules in two subjects, and no effects in three other subjects. Application of dimethyl-para-phenylenediamine in the same way for thirty minutes produced no effects on five subjects.

Prevention and Treatment of Skin Lesions.—The influence of various lipoid solvents on the irritant properties of dimethyl-para-phenylenediamine was tested, with the idea of using the most suitable solvent in the prophylactic treatment of workers with this compound. Five per cent. concentrations of the dimethyl derivative in cotton-seed oil, in 98 per cent. alcohol, in turpentine, and in 5 per cent. castile soap were made and applied directly to areas 2 cm. in diameter on the skins of forearms of the same subjects used in the experiments described above. As a control, 0.002 c.c. of the compound itself was applied to each forearm. The control and soap solution produced the usual effects consisting of burning, tenderness, erythema, discoloration, and blisters, while the oil, alcoholic, and turpentine solutions produced no demonstrable effects for three days after application, and the subjects were dismissed. Two subjects reappeared on the eighth day, however, and two on the thirteenth day after application, with the usual signs and symptoms of dermatitis, including blisters in the areas where the alcohol, oil, and turpentine solutions had been applied. Meantime, the control and soap areas had practically healed. The development of latent dermatitis is not peculiar to these compounds, but was observed also with mustard gas and other irritants during the late war.

Similar results were obtained on a dog whose shaved skin was painted in several places with the same solutions and control that were used on the human subjects. The control and soap areas showed the presence of erythema and urticaria before the areas that were painted with alcohol, turpentine, and oil solutions. In other words, soap, as compared with other solvents, facilitated the production of dermatitis presumably because of the increased lipoid solubility of the irritant or emulsification of skin lipoids with it. It would, therefore, be useless as a detergent for the removal of dimethyl-para-phenylenediamine under industrial conditions.

The results obtained show that soap and the lipoid solvents that were tried do not interfere with the development of dermatitis from dimethyl-para-phenylenediamine. Rubbing the skin with these solvents was also tried, but was found to be ineffective for complete prevention of the dermatitis after itching once started. The most efficient solvent for removal of the irritant was found to be acetic acid which can be used in high concentrations (up to 50 per cent.), and which converts it into a soluble acetate. This is the choice solvent for industrial purposes. After itching has definitely begun, however, acetic acid is

also without influence on the urticaria and vesication which usually follow.

The pruritus after the application of dimethyl-para-phenylenediamine, or after the handling of articles containing it, was rather marked. The following alleged antipruritic agents were, therefore, applied locally and in liberal quantities: 25 per cent. magnesium sulphate; 2 per cent. ammonia; 10 per cent. benzyl alcohol in lard; and benzyl alcohol, full strength. All of these measures gave temporary relief, that is, immediately after application and for about five minutes, but after that itching continued as usual. Plunging or bathing the parts in cold water gave as good relief as any of the preceding measures.

Variability of Human Skin.—The response of different human skins to these compounds differed. Under the conditions, it was impossible to ascertain the extent of the variability, but a few preliminary trials were made, using the method of Marshall, Lynch, and Smith (35). That is, a series of different concentrations of the compounds were made in petrolatum liquidum and were applied to areas of about 1 cm. in diameter on the forearms of six subjects. The concentrations of the dimethyl derivative used ranged from 0.01 per cent. to 5 per cent. The lowest effective concentration, as indicated by redness and local heat in three subjects, was 0.1 per cent., and in three others it was 1 per cent. Another subject, a worker with this compound, was found to respond invariably to a 0.01 per cent. concentration. The concentrations of the diethyl derivative ranged from 0.1 per cent. to 10 per cent. The lowest effective concentration in one subject was 0.2 per cent., and the remaining five subjects failed to give responses with the strongest (10 per cent.) solution used. It is obvious, therefore, that there is considerable variation in the response of different human skins to the dimethyl and diethyl derivatives, when they are dissolved in petrolatum liquidum. The study could not be pursued further for the lack of subjects.

Antagonism to Dichlorethylsulphide.—The dimethyl and diethyl derivatives of para-phenylenediamine possess certain properties which might make them useful as preventives or adjuvants in the treatment of burns from dichlorethylsulphide (mustard gas). That is, they are lipoid soluble bases and penetrate the skin readily, and they also react readily with acids forming salts which are non-irritant as far as skin is concerned. Assuming that the mechanism of the action of dichlorethylsulphide as explained by Lynch, Smith, and Marshall (36) is correct and consists of an intracellular acidosis, due to the liberation of hydrochloric acid, the direct application of a base like dimethyl-para-phenylenediamine should mitigate the local irritant action of the dichlorethylsulphide to some extent at least. The chief disadvantage with dimethyl-para-phenylenediamine is its systemic toxicity from rapid skin absorption. Nevertheless, several attempts were made to treat mustard gas burns produced on the shaved skins of rabbits. The dimethyl-para-phenylenediamine was applied directly to the areas treated with mustard gas. The results were disappointing. Small quantities of dimethyl-para-phenylenediamine were ineffective, and large quantities (0.002 c.c. and over per square centimeter of skin per kilo body-weight) killed the animals. In some animals there appeared to be some retardation in the development of burns, in comparison with the controls, but in the end the ef-

fects of dichlorethylsulphide prevailed. Although these results are negative, they may be of interest to those working with toxic war compounds, since it may be possible to modify the toxicity of certain phenylenediamines and yet preserve their lipoid solubility and render them suitable for treating lesions caused by dichlorethylsulphide and similar compounds.

Blood.—Direct inspection of the skin, after the application of both dimethyl-para-phenylenediamine, and diethyl-para-phenylenediamine, indicated that irritation took place independently of precipitation in the tissues. It is difficult, however, to recognize moderate protein precipitation in this way, and the compounds were therefore added directly to diluted blood and serum. It was found that 1 per cent. concentrations of the bases in 0.9 per cent. sodium chloride solution did not precipitate 10 per cent. dog's blood and serum (also in 0.9 per cent. sodium chloride). There was also no hemolysis, but all mixtures were darker than control dilutions of untreated blood and serum. The presence of methemoglobin in these mixtures could not be established spectroscopically. The hydrochlorides of all phenylenediamines are acid in reaction, possess an astringent taste, and precipitate serum. This is due to the acidity.

3. *Symptoms and Production of Edema and Effusions*

The symptoms produced by hypodermic and gastric administrations of the phenylenediamines are quite similar as far as changes in respiration, pulse rate, body temperature, reflex excitability, and convulsions are concerned. The various compounds differ sufficiently in the production of edemas and effusions to require brief descriptive summaries of their actions. The effects were studied on several different species. The pulse and respiratory rates and rectal temperature were obtained in the usual way.

Meta-Phenylenediamine.—This compound was administered in the form of hydrochloride to six rabbits, ten white rats, one dog, and one cat. The dosage for rabbits ranged from 0.1 gm. to 0.4 gm. per kilo; for rats, from 0.06 gm. to 0.4 gm.; for the dog it was 0.2 gm.; and for the cat, 0.4 gm. The effects of hypodermic and gastric administrations were the same and have been grouped together. The onset of symptoms with gastric administration was slower, however, as would be expected. There was invariably an increase in pulse and respiratory rates and a slight increase in rectal temperature (0.1 to 0.5° C.). With fatal doses, the animals showed tremors, increased excitability, convulsions of meduliary and spinal types, marked depression, cyanosis, collapse, and death. Only two rabbits and one rat recovered. The remaining animals died at varying intervals, but as a rule the effects were fatal not later than the day following the administration of the compound. No edemas of the face, conjunctiva, neck, or tongue were observed in any of the animals. At autopsy, the most characteristic change that was found was hydrothorax, but it was also variable. Hydrothorax was definitely present in three rabbits that received 0.2 gm. of the compound per kilo, and absent in two rabbits that received 0.1 gm. and one rabbit that received 0.2 gm. per kilo. It was also present in the cat which received 0.4 gm., but absent in the dog which received 0.2 gm. per kilo. The hydrothorax was always bilateral, and the volume of fluid in the rabbits and in the

cat ranged from 2 to 5 c.c. per pleura, or a total of 4 to 10 c.c. from both pleural cavities. The fluid was clear and colorless. No examination was made for the presence of formed elements. Negative chemical tests with sodium nitrite indicated the absence of meta-phenylenediamine. The abdominal viscera of those animals which showed no hydrothorax appeared rather wet and shiny, but it was impossible to measure the fluid in order to gain a definite idea of the change in fluid volume in the peritoneal cavity as compared with the normal, which is usually too small in volume to be measured. There may have been hydroperitoneum, but it certainly could not be as clearly demonstrated as the hydrothorax.

Other changes at autopsy consisted of marked visceral congestion and edema of one or both lungs in some, but not all, animals. Fresh autopsies indicated unusually active peristalsis of the intestines and contraction of the bladder. In the ten white rats that were studied, hydrothorax, hydroperitoneum, and facial edema were not demonstrable. As far as facial edema is concerned, my results agree with those of Meissner (25), but disagree with the positive result of Hess and Müller (26) in the one rat which they observed. As for hydrothorax, and possibly hydroperitoneum, in rabbits, my results agree with those of Hess and Müller.

Para-Phenylenediamine.—This compound was administered in the form of base and hydrochloride to ten rabbits, ten white rats, and one cat. The range of dosage for rabbits was from 0.1 gm. to 0.45 gm. per kilo; for white rats, from 0.075 gm. to 1.0 gm. per kilo; and for the cat 0.1 gm. per kilo, administered by stomach and subcutaneously. The symptoms by both methods of administration were the same, the time of onset and progress being more rapid with hypodermic administration. All animals showed an increase in pulse and respiratory rates, and the cat and rabbits showed a fall of temperature about fifteen to thirty minutes after administration. With non-fatal doses the respiration became very rapid, dyspneic, and accompanied by loud wheezing which was audible at a distance of 30 feet with some animals. At the same time there was an increase in secretions from the mouth, nose, and eyes. At the end of one and one-half to four hours swelling of the nose, lips, tongue, orbital tissues, conjunctiva, and neck was observed. Facial, tongue, and neck edemas were observed in four rabbits receiving from 0.2 gm. to 0.22 gm. per kilo by stomach and subcutaneously. Edemas were absent in six rabbits receiving from 0.1 gm. to 0.45 gm. per kilo by stomach and subcutaneously. With the higher doses, death supervened before the edema could develop. Figure 1 illustrates edema of the face, tongue, and nose in a rabbit after the administration of para-phenylenediamine hydrochloride.

The facial and neck edemas were characterized by rather pronounced, pouchy and soft swelling. The lips were very thick and the skin of the neck was pendant. The tongue was so swollen that it protruded from the mouth. Erdmann and Vahlen attributed the marked dyspnea to obstruction in the pharynx and glottis by the swollen tongue. The orbital tissues and conjunctiva were so swollen that they gave the appearance of exophthalmos. When the effects occurred, they were indeed very striking and unmistakable, but some rabbits showed no demonstrable edemas or ef-

fusions anywhere. At autopsy, the rabbits which showed facial and cervical edemas showed no hydrothorax nor hydroperitoneum. The ten white rats which were injected with doses ranging from 0.075 gm. to 1 gm. per kilo showed no edemas nor exudations anywhere. All the rabbits which showed edemas of the face and neck died eventually, although recoveries from the acute edema and other symptoms occurred. The edemas were most pronounced on the day following administration, less pronounced on the third day, and complete recovery took place by the end of the sixth day. One animal died on the sixth, one on the eighth, and one on the thirteenth day after administration. Apparently there was permanent injury to important functions and organs even in those animals which recovered from the acute effects.

The results that were obtained with para-phenylenediamine administered to rabbits and a cat are confirmative of those obtained by previous investigators. The results of previous investigators show that dogs give practically the same response as cats and rabbits. Reports in the literature give the impression that rabbits respond uniformly to the production of edema. The results here reported do not sustain this belief, however, and white rats failed to show evidences of edema. It is concluded, nevertheless, that a certain proportion of rabbits responds to the administration of para-phenylenediamine with a peculiar and marked edema of the face, tongue, conjunctiva, and neck. On the other hand, a certain proportion of rabbits responds quite differently to meta-phenylenediamine — namely, with hydrothorax, and possibly with hydroperitoneum. The production of marked pulmonary edema does not seem to be a prominent feature in the actions of these compounds. Moderate degrees of pulmonary edema could not be detected under the conditions of the experiments.

Dimethyl-Para-Phenylenediamine and Diethyl - Para - Phenylenediamine. — These two compounds gave practically identical results as far as symptoms were concerned; the diethyl compound, however, being less toxic, required larger dosage than the dimethyl compound. Dimethyl - para - phenylenediamine was administered by stomach and hypodermically to four rabbits, two guinea-pigs, one cat, and fourteen white rats. For rabbits the range of dosage was from 0.06 gm. to 0.3 gm. per kilo; for guinea-pigs, from 0.03 to 0.6 gm.; for the cat, 0.02 gm.; and for the rats, from 0.063 to 0.3 gm. Diethyl-para-phenylenediamine was administered in the same way to six rabbits, three guinea-pigs, two cats, and fifteen white rats. The range of dosage was from 0.05 gm. to 0.4 gm. per kilo for the rabbits; 0.03 gm. to 0.2 gm. per kilo for the guinea-pigs; 0.05 gm. and 0.3 gm. per kilo for the two cats, and from 0.013 gm. to 0.3 gm. per kilo for rats.

In rabbits, cats, and guinea-pigs, both compounds caused a prompt increase in respiratory and pulse rates, the increases being somewhat more uniform and pronounced with the dimethyl compound than with the diethyl compound. Rabbits showed a fall in rectal temperature, except when convulsions occurred; then the temperature rose. It fell again, however, when the convulsions stopped. Cats responded more uniformly with a fall in temperature. The rabbits and rats which died as a result of the administration of these compounds showed increased reflex excitability, tremors, convulsions of medullary and spinal types, marked cyanosis, very rapid respiration, marked motor depression, coma, further fall in body temperature,

and death. None of the animals exhibited edemas anywhere. Most of the rabbits and guinea-pigs and all the cats died very soon or eventually after the administration of the compounds. White rats showed a mortality of about 50 per cent., depending on the dosage.

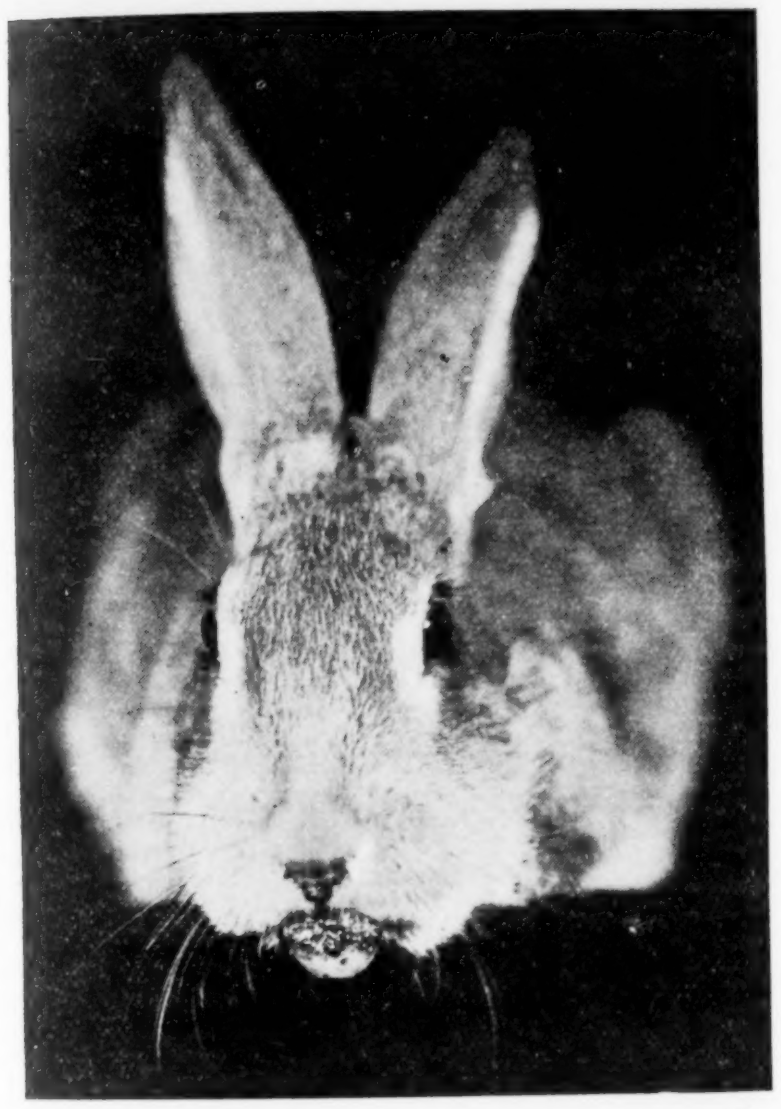


FIG. 1.—Edema of tongue, nose, and face following administration of 0.2 gm. of para-phenylenediamine per kilo by stomach to a rabbit (1.2 kg.). Before administration, the pulse rate was 212, the respiratory rate, 84 per minute. Four hours after administration of the agent the pulse rate was 300, the respiratory rate 60. Other symptoms were: dyspnea, marked exophthalmos, and chemosis, facial edema, nose large, tongue hanging and markedly swollen. The rabbit had recovered completely from the edemas at the end of six days; it died of pneumonia and pulmonary edema at the end of thirteen days.

These animals were also used for the determination of fatal dosage of these compounds as described in the beginning of the paper.

At autopsy, the only noteworthy changes consisted of marked congestion of all viscera, marked intestinal peristalsis, and very dark blood. There were no evidences of hydrothorax or hydroperitoneum.

The results obtained agree with those of Meissner's experiments with dimethyl-para-phenylenediamine on rabbits, but do not support his claim that diethyl-para-phenylenediamine causes facial and cervical edema. The reason that edema does not occur after the administration of dimethyl-para-phenylenediamine is because the compound is markedly toxic and death results before the edema process is fully developed; small quantities, that is, less than toxic amounts, are inadequate for the production of edema. On the other hand, diethyl-para-phenylenediamine is no more toxic than para-phenylenediamine, which produces edema in some rabbits. Other factors, as, for instance, altered concentration of the blood, which may be concerned in the production of edema even before it is grossly recognizable, were not studied.

Mechanism of the Production of Edemas and Effusions.—It was thought more desirable to determine the incidence of the edemas and to obtain some idea of the ordinary pharmacological actions of the phenylenediamines before proceeding to a detailed study of the mechanism of the edemas and effusions. The edemas are undoubtedly among the most interesting features in the actions of these compounds. Certain evidences in the literature indicate that the edemas and effusions caused by these compounds are associated with an increase in permeability of the capillaries. It is not indicated, however, why para-phenylenediamine appears to have a predilection for the head and neck, and meta-phenylenediamine for the pleura and peritoneum. The vascularity of certain parts, and the circulatory stimulant properties of the compounds (to be described) would favor the production of edemas and effusions. I have already indicated that volatility

and lipoid solubility play a definite rôle in the predilection of the dimethyl and diethyl compounds for the skin. The rôle of quinonediimine is not established. Section and degeneration of sympathetic nerves do not prevent the edemas. Other possibilities are deprivation of oxygen in the tissues and local acidosis.

4. *Action on Frogs*

The effects of the phenylenediamines on frogs are different from those on mammals. The meta and para compounds cause gradual depression, with muscular relaxation and paralysis (Meissner; Matsumoto). Previous to the present investigation the dimethyl and diethyl derivatives of para-phenylenediamine had not been studied. Fatal and non-fatal doses of these compounds were therefore injected into the anterior lymph sacs of frogs, and the effects observed. Six frogs were injected with the dimethyl derivative, and four with the diethyl derivative. Both compounds gave the same results. The following protocol of an experiment with the dimethyl derivative indicates the effects, and results of analysis of the depressant action.

PROTOCOL.—Frog. 29 gm.

2:17.—0.03 c.c. of 1 per cent. solution of dimethyl-para-phenylenediamine per gram of weight injected into anterior lymph sac.

2:37.—Marked depression; frog sat and refused to move; no increase in reflex excitability. Animal sank in water; made attempts to swim but did not succeed in reaching the air.

3:10. — Complete muscular relaxation; when put on its back, frog lay in place; no convulsions at any time.

Heart dilated and still beating, although very slowly. Blood was very dark. Sciatic nerve and gastrocnemius muscle responded to electrical and mechanical stimuli. The central nervous system was exposed, and weak faradic stimulus was applied from above downward; there was no response by stimulation of cerebral hemispheres in different regions; prompt muscular responses occurred, however, when the same stimulus was applied to the optic thalamus, optic lobes, medulla, cord, and sciatic plexus. The depression appeared, therefore, to be above the optic thalamus.

The results with the remaining frogs were similar, and agreed with those obtained by Meissner and Matsumoto in their experiments with meta-phenylenediamine and para-phenylenediamine on frogs. Briefly summarized, the effects of these compounds on frogs consist of gradual motor depression, marked discoloration of the blood, circulatory collapse, and death. At autopsy the hearts of those animals which died from the effects of the poisons were markedly dilated and refractory to direct mechanical and electrical stimuli. Convulsions were absent even in those animals which received fatal doses. In fact, there was produced a depression similar to that caused by morphine or narcotics, and later a paralysis of such a degree that the animals were not able to perform purposive movements: the effects corresponded to those following ablation of the hemispheres. It was shown that the different portions of the central nervous system from the optic thalamus to the spinal cord, inclusive, and the peripheral nerve trunk, nerve endings, and skeletal musculature were not paralyzed by the highest doses. It was, therefore, concluded that the depression was central in the hemispheres and resembled that produced by morphine. None of the animals used in these experiments showed increased excitability or convulsions. Apparently the main action on the nervous system in frogs was depressant; the stimulant action, if any, was evanescent. It will be seen later that the smooth muscle of excised organs in frogs is markedly stimulated

by the phenylenediamines. It will also be seen that the terminal depressant action upon the circulation is the same in mammals as in frogs. All these findings indicate that the actions of the phenylenediamines are complex.

5. *Convulsant Action in Mammals*

The results obtained with frogs do not throw any light on the cause of the convulsions which occur in mammals, because the predominant action of the phenylenediamines upon the nervous system of frogs is paralysis. The clonic nature of the convulsions in mammals indicates that these are not due to direct muscular (veratrin-like) stimulation. Two other important possibilities remain: (1) that there is direct and more prolonged stimulation of the central nervous system (cerebrum, medulla, and cord) of mammals than of frogs; (2) that asphyxia occurs from alteration of the blood pigment by the compounds, or gradual circulatory depression. Asphyxia may be ruled out at once, because the administration of artificial respiration to operated and unoperated rabbits, cats, and dogs did not prevent the convulsions. Furthermore, the onset of convulsions was rapid, taking place twenty to thirty minutes after application to the skin of rabbits, and after hypodermic injection in white rats, cats, and rabbits, and almost immediately after the intravenous injection of large doses in dogs and cats. Under these conditions, the convulsions continued for some time (from one to one and one-half hours) and increased in severity before cyanosis was evident, although some difficulty was experienced in interpreting this properly because of the dark discoloration of the blood produced by the compounds themselves. The presence of methemoglobin was not established in any of the bloods of the different species studied. Its presence in the blood of animals dying from the phenylenediamines is denied by Meissner and Erdmann and Vahlen. The discoloration was apparently due to the oxidation product of the phenylenediamines, namely, quinonediimine, which does not *per se* contribute to or cause asphyxia. This leaves direct stimulation of the nervous system by the phenylenediamines themselves as the cause of the convulsions. Both the medullary and spinal types of convulsions were observed and it may be assumed, therefore, that both the medulla and cord are involved in the stimulation.

(To be continued)

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OBSERVATIONS UPON THE EFFECTS OF EXPOSURE TO ARSENIC TRICHLORIDE UPON HEALTH

(Continued)

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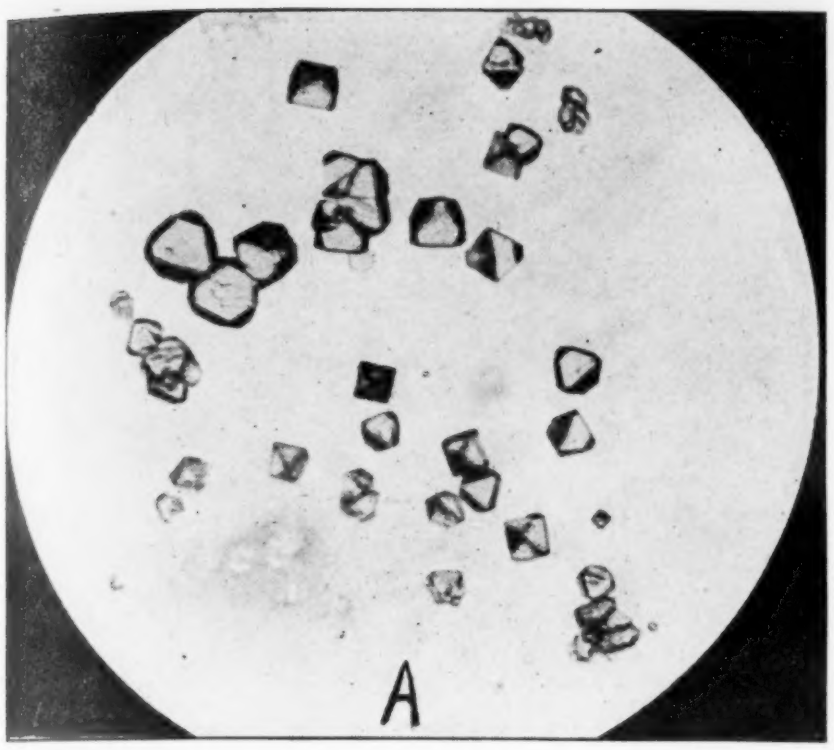
PHENOMENA OBSERVED WHEN ARSENIC TRICHLORIDE IS EXPOSED TO AIR

A. Arsenic trichloride exposed to air dried over sulphuric acid and confined in a bell jar of moderate size evaporated fairly rapidly without undergoing any obvious change, and without causing any cloudiness of the air or producing any perceptible deposit upon glass plates exposed in a chamber; ¼ c.c. of the arsenic trichloride had almost entirely disappeared in twenty-four hours. The thin layer remaining in the watch glass did not alter in appearance in the course of five days, but at the end of that time it was syrupy in consistency and on being exposed to ordinary air it became opaque and white. Very few microscopic granules were recognizable on the surface of a glass plate exposed in the chamber. The sulphuric acid contained a large amount of arsenic.

B. Arsenic trichloride exposed to air saturated with water confined in a bell jar of the same size as that used in Experiment A behaved quite differently. The air of the jar became rapidly cloudy, and the glass surfaces exposed to this cloudy air were soon coated with a thin white deposit. Ten minutes later the air was still cloudy and minute dew-like drops had formed upon the marginal part of the watch glass containing the arsenic trichloride, and also upon the surface of the glass plates exposed in the jar as well as upon the sides of the jar itself.

After four hours, changes which have already been described were observed in the arsenic trichloride. The droplets formed among the white deposit on the glass surfaces had increased considerably in size. After twenty-four hours, the arsenic trichloride had increased slightly in bulk. The white deposit on the glass plate examined under the microscope consisted of semi-crystallized granules of small size. In the large clear drops of fluid which had formed at fairly regular intervals among this deposit, there were large transparent crystals, some of which were clearly octahedral. (See Fig. 3.) At the end of five days, the bulk of the fluid contained in the watch glass was about five times that of the arsenic trichloride originally placed in it. An abundant semi-crystalline deposit had formed in this fluid. The water in the dish placed in the jar contained a large amount of arsenic as did also the deposit on the glass plates. Notwithstanding these great differences, it is clear that arsenic trichloride emits gases rich in arsenic whether it is exposed to dry or to moist air. (See also animal experiments 17 and 19.)

Arsenic trichloride, 0.98 gm., contained in a watch glass (the surface of the fluid measuring about 7 cm. square) supported by one arm of a special balance was placed under a bell jar of a capacity of about 20,000 c.c. The air of this jar was partly dried by sulphuric acid. Test plates A, B, and C were supported at various heights in the vessel, which was hermetically closed by a glass plate to which it was luted. (See Fig. 4.)



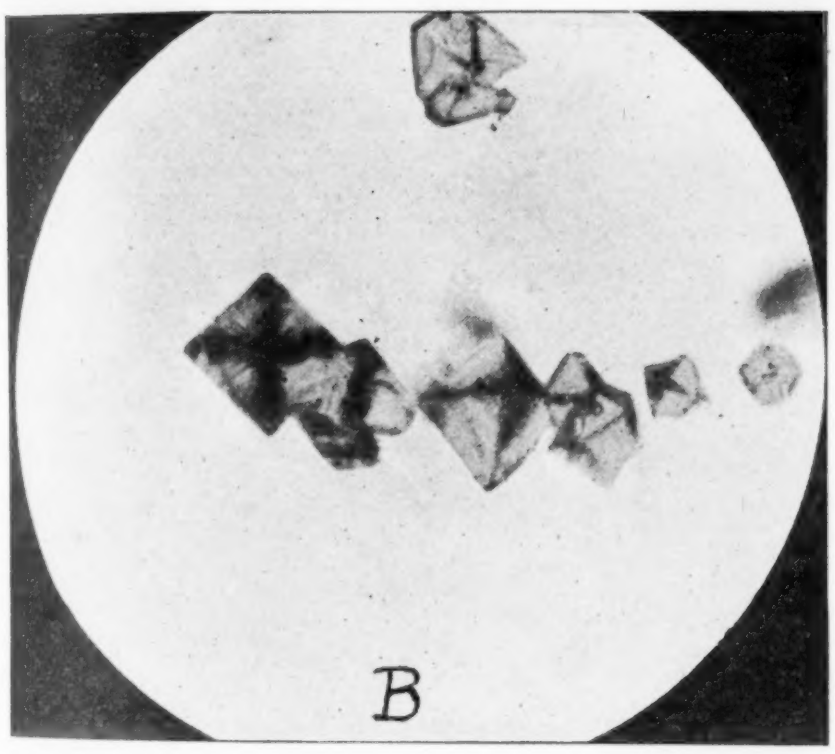


FIG. 3.—Deposit produced by arsenic trichloride in presence of water vapor. (X 175.) A and B=octahedral crystals formed in the droplets of fluid.

emit any visible fumes, but after several minutes a slight cloudiness was visible in the upper part of the jar and within thirty minutes the whole jar was full of minute particles in active motion, and a white film had formed on each of the test plates A, B, and C. These particles were barely visible to the naked eye, but with the help of a magnifying glass and of a suitable light their motion could be clearly followed. They formed at a short distance above the watch glass containing arsenic trichloride, then rose rapidly to the dome of the jar (*i.e.*, to a height of about 35 cm.). They then dispersed in different directions, forming various streams, and fell down along the sides

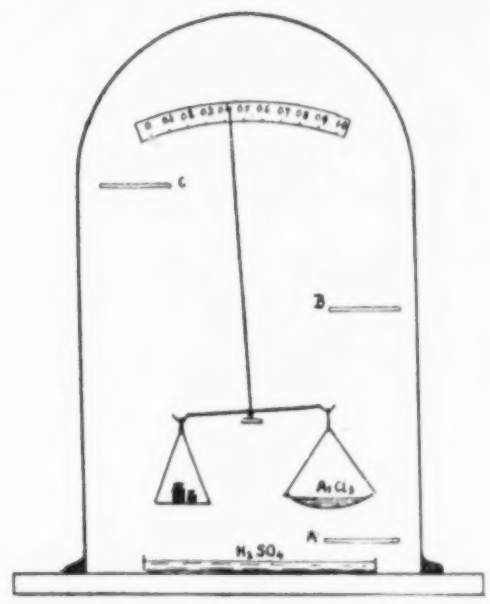


FIG. 4.—Bell jar (22,000 c.c.) showing arrangement adopted for estimating rate of volatilization of arsenic trichloride in air dried by sulphuric acid. A, B, and C=test plates. (Scale 1 to 13.)

During the first hour 0.18 gm. of the arsenic trichloride became gaseous; the fluid in the watch glass lost weight more slowly afterwards, about 0.4 gm. being lost in the twelve hours following the first, and about 0.2 gm. in the subsequent eleven hours. The total loss in twenty-four hours was, therefore, about 0.78 gm., or on an average of 0.0325 gm. per hour. Over one-quarter of the amount lost in twenty-four hours had volatilized during the first hour.

The air of the jar remained clear at first and the arsenic trichloride did not of the jar, some of them reaching the bottom. They rose again toward the watch glass, however, and joined the stream of particles arising from the arsenic trichloride. This circulatory motion appeared to be determined by the relative temperature of the air above the watch glass and of that near the walls of the jar. The heat thrown against the sides of the jar by an ordinary incandescent electric lamp, situated at some distance from the jar, was sufficient to divert the stream of particles toward the light. The heat of the hand applied to one side of

the jar had the same effect. The presence of the trace of water remaining in the air appeared to be necessary to the formation of a solid oxychloride of arsenic. The first ascent of the particles was obviously caused by the warming of the air due to the heat of combination. As the warm air over the watch glass rose, it carried with it the light particles as they were formed. On reaching the top of the jar, however, this air was cooled and, being displaced by more warm air, streamed down the side of the jar from which it returned to the neighborhood of the watch glass to replace the rising warm air. At the end of the experiment the upper surface of each of the test plates was covered with a white deposit. This phenomenon is not only interesting from a scientific point of view, but is of importance as indicating a method for the removal of arsenic trichloride fumes.

When ammonia is present in air to which arsenic trichloride is exposed, white fumes are also produced owing to the formation of the chloro-ammonio-arsenical compound or compounds already alluded to. These fumes are composed of solid particles which form denser and more distinct clouds than those of the oxychloride; they are subject to the same movements as those which have been previously described. Advantage was taken of the greater visibility of these fumes to take photographs showing some of the phases of the phenomenon. (Fig. 5.)

A shallow rectangular case was constructed by fixing together sheets of plate glass. Through two small doors at the ends of the base plate, two capsules containing respectively 1 c.c. of arsenic trichloride and 5 c.c. of weak ammonia solution were introduced almost simultaneously. A powerful beam of light was thrown through the glass case and photographs were taken at intervals.

Figure 5A shows the appearance of the glass case immediately after the introduction of the capsules of ammonia (left), and arsenic trichloride (right). The arc lamp was at the right of the case. For the first two or three minutes very little change was observed, then a small cloud formed over the arsenic trichloride and began to rise rapidly to the top of the chamber (about 35 cm.).

Figure 5B was taken five minutes after the beginning of the experiment. The column was deflected toward the light owing to the current of warm air caused by the heat of the lamp (although a trough of water had been interposed to absorb the greater part of the heat). In addition to the main ascending current, a much smaller descending current was noticeable.

Figure 5C was taken ten minutes after the beginning. The fumes, after flowing under the top plate toward its left end, had turned downward along the colder left side of the chamber, and when near the base had flowed along the base toward the right, generally rising before reaching the ascending stream above the capsule of arsenic trichloride. This stream of fumes was composed of subsidiary streams which on expanding produced the clouds visible in the photograph.

Figure 5D was taken fifteen minutes after the beginning. The whole chamber was then full of white fumes, densest on the right over the arsenic trichloride, from which fresh fumes continued to rise.

Figure 5E was taken thirty minutes after the beginning of the experiment, when the fumes had ceased to rise in a continuous stream; a dense cloud hung over the arsenic trichloride, from which fresh fumes burst at intervals. The

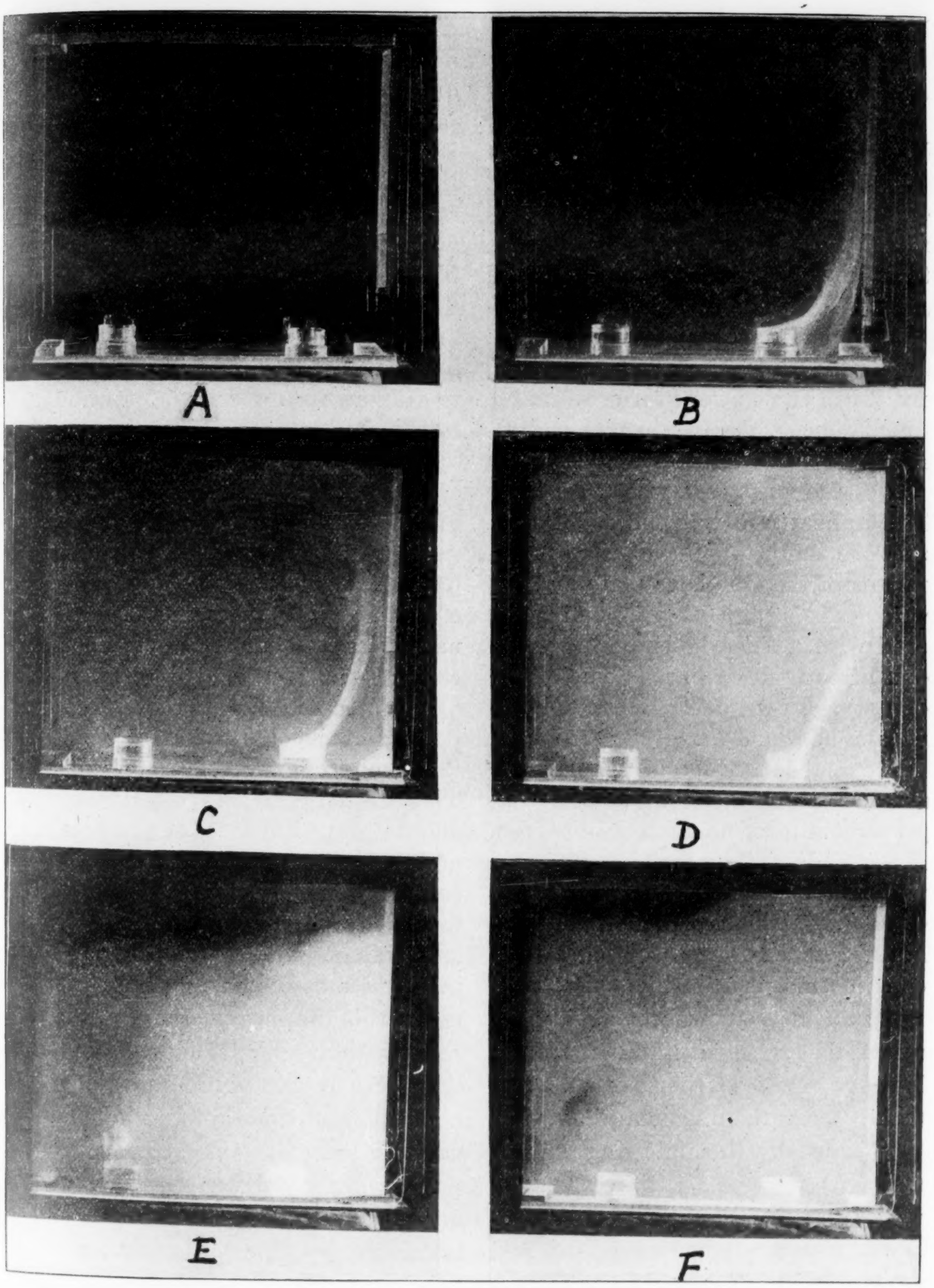


FIG. 5.—Production and distribution of arsenic trichloride fumes. · A=beginning of experiment, B=five minutes after beginning, C=ten minutes after, D=fifteen minutes after, E=thirty minutes after, and F=one hour after beginning.

fumes in the upper part of the chamber had begun to settle, falling upon the bottom plate in the form of very fine white granules (semi-crystalline under the microscope).

Figure 5F was taken one hour after the beginning. After a final outburst of fumes, the aerial precipitate had begun to fall so abundantly upon the base plate as to cover it entirely with a white opaque layer which is visible in the photograph. The arsenic trichloride capsule had become visible again and very little, if any, fresh fumes were formed. After two hours more, the precipitate had almost entirely settled; twelve hours later the air of the glass case was quite clear and its appearance was the same as it was before the beginning of the experiment, except that the base plate and the upper surface of objects lying on it were covered with a thick layer of the white deposit already described. Some of the deposit was given to Mr. Heap for analysis, and he found that it differed from the white deposit formed in the presence of air and water alone in that it contained a definite proportion of nitrogen.

At the end of this experiment some arsenic trichloride remained in the capsule and was still capable of emitting fumes. It seemed, therefore, that a state of combination equilibrium had been brought about somewhere about the mouth of the vessel containing arsenic trichloride. Outside this area the air was saturated with ammonia. This view was confirmed by the following experiments:

Two small cups containing respectively 0.5 c.c. of dilute liquor ammoniae and 0.5 c.c. of arsenic trichloride were introduced simultaneously into the lower part of an hermetically sealed jar (24 cm. in diameter and 48 cm. in height). After a few minutes the fumes began to rise above the cup of arsenic trichloride and phenomena similar to those previously described were observed. The cup of ammonia was removed when the whole jar was full of dense white fumes. These had entirely settled three hours later, the bottom plate and test plates being covered with a thick white deposit. The air of the jar was saturated with invisible arsenic trichloride vapors. The cup of arsenic trichloride was then removed and the cup of ammonia returned to its original position. Dense fumes began to rise at once over this cup and after thirteen minutes the whole jar was filled with dense white fumes, which settled down within three hours, leaving the air of the jar quite clear. The jar was now saturated with invisible ammonia vapors. This experiment was repeated several times with the same results. Ultimately the arsenic trichloride cup was closed by a thin solid diaphragm (Fig. 6) fixed to the lips of the cup and suspended at a height of 1 to 2 cm. above the level of the fluid arsenic trichloride. This diaphragm was much convoluted and its shape indicated the intermittence and variations in the intensity of the combination. It had obviously been formed in the plane where the gaseous ammonia and arsenic trichloride had met in suitable combining proportions. Beneath this diaphragm the air was saturated with arsenic trichloride; outside it there was an excess of ammonia.

Moist air containing ammonia was used in these last experiments for the purpose of studying the behavior of arsenic trichloride vapors more closely than was possible when air containing only water vapor came into contact with arsenic trichloride. The object of this study was to find some means of bringing arsenic trichloride fumes under control.

When a current of dry air is caused to pass over the surface of arsenic trichloride, evaporation of the fluid takes place rapidly without alteration in the appearance of the fluid. When the air is moist, the arsenic trichloride becomes rapidly turbid, and after a time a thin layer of clean watery fluid forms on its surface.

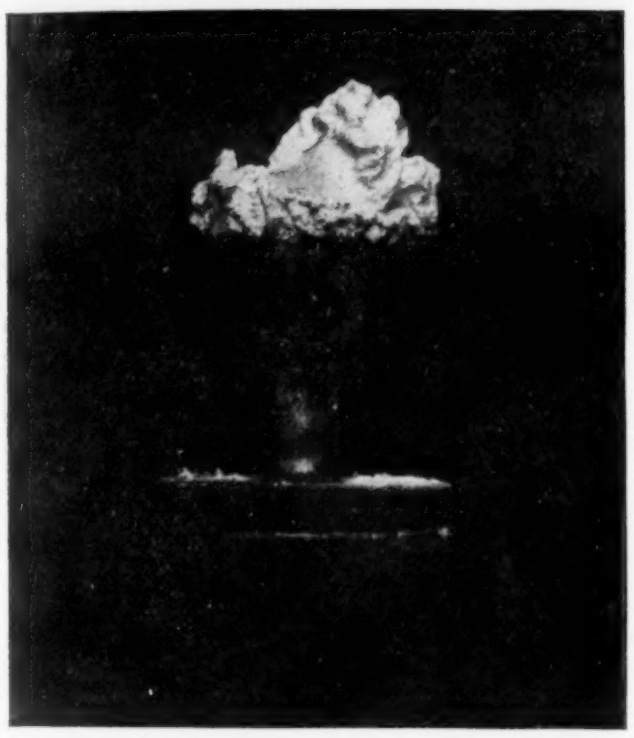


FIG. 6.—Solid diaphragm formed in plane of saturation between ammonia and arsenic trichloride vapors. (Normal size.)

The cup is filled with arsenic trichloride vapors generated by a few drops of arsenic trichloride at the bottom of it; the air outside the cup is saturated with ammonia.

When a current of air laden with arsenic trichloride is admitted to a chamber, such as the 215,000 c.c. chamber used in the animal experiments, a cloud is produced near the inlet. This cloud is densest at some distance from the inlet and extends in the direction of the outlet. As it extends, it first rises to the upper part and then gradually falls down in the outlet part of the chamber. The air at the sides of the inlet remains generally clear, or almost clear. The density of the fumes is, therefore, greater in the middle and outlet parts of the chamber than in the inlet part, except near the inlet in the path taken by the fumes. Test plates placed in various parts of the chamber show deposits of various density which indicate the same irregularity of distribution. These observations explain why animals placed in different parts of the chamber are unequally affected by the fumes (see Experiments 11, 12, 13, and 14).

These facts show that arsenic trichloride is very diffusible and enters readily into various combinations when it comes into contact with air containing moisture. The resulting oxychloride is precipitated in the form of fine, snow-like flocculi which are initially so light that the heat generated at the time of combination is sufficient to induce air currents which carry the precipitate to a considerable height, from which it afterwards falls as a kind of snow and covers the upper surface of all the objects exposed to it.

A considerable part of the evaporated arsenic trichloride is disposed of in this way; many of the outlying and apparently heavier particles do not rise with the main stream, however, but fall more or less rapidly to the ground over which they spread gradually. In addition to these visible particles, there is evidence of the presence of invisible vapors of arsenic trichloride when the air is unsaturated with water.

It is obvious that where the amount of air is unlimited there is enough moisture in it to convert the invisible vapors of arsenic trichloride into visible fumes which are not very distinct when the air is nearly dry, but which are very conspicuous when the air is saturated with water. In very dry localities, however, arsenic trichloride might diffuse indefinitely without any visible trace of its presence being noticed, except at places where it came into contact with damp or wet surfaces (such as the mucous membranes of men or animals), or with

moist air, such as expired air.

It is clear that the precipitate of oxychloride and allied products which form in the air have a great tendency to cling to the surface of solid objects with which they come in contact. This is one of the reasons why the hair of persons working in arsenic trichloride plants becomes so rapidly laden with arsenic. Arsenic trichloride is also rapidly absorbed by animal tissues.

Detection of Arsenic Trichloride or Derivatives in the Air of Places Where Arsenic Trichloride Is Prepared or Handled

A previous investigation[2] had shown that the hair of persons and the leaves of plants exposed to arsenical fumes, such as may be generated during the combustion of coal and coke, become loaded with arsenical deposits which can be detected by a suitable method such as the hydrochloric-copper method already described. The hair of persons working in arsenic trichloride plants might, therefore, be expected to give an indication of the extent of their exposure. It appeared desirable to examine the urine also in order to ascertain whether arsenic was absorbed by the lungs, skin and mucous membranes, and excreted by the kidneys.

The results recorded in Table 5 leave no doubt as to the serious extent to which persons working in, or in connection with, arsenic trichloride plants are exposed. Few of the cases investigated show clear evidence of arsenicism, and where such a state was indicated the symptoms were generally slight. The amount of arsenic found in the hair bore a distinct relation to the amount of exposure. The examination of the hair, therefore, supplies valuable information.

Visit to Factory. — The plant inspected consisted of six retorts with condensers housed in a shed open on all sides. The openings through which the retorts were fed were situated on a long upper platform. Four of the retorts were of an old type, the other two were of a new type and there was room on the platform for two more of these new type retorts. Contiguous and parallel to this upper platform, but at a lower level, there was another platform on which arsenic trioxide and chloride of sodium were kept ready for mixing. The retorts and furnaces were situated immediately below the upper platform and from the bottom of each retort there was a conduit taking the residue from the retorts to trucks. On the other side of the retorts, raised slightly above the ground, there was a large tank used for storing arsenic trichloride, and close to this tank there were rows of iron drums filled with arsenic trichloride ready for shipping.

The most striking difference between the old and the new retorts was in their connection with the condensers. From the old retorts the products of distillation rose first through a tall vertical pipe, and were then directed by a horizontal pipe to a lead coil cooled by water contained in a large tank situated at the side of the upper platform. The condensers connected with the new retorts were situated on the upper platform, above the retort, and the pipe bringing the volatile products to the lead coil was entirely surrounded by the condenser. As the products of distillation issued from the condenser they passed through a small separating chamber from which arsenic trichloride and hydrochloric acid issued by sepa-

[2]Arsenic in Modern Life. Jour. Roy. San. Inst., 1902, *23*, 244.

TABLE 5.—RESULTS OF EXAMINATION OF HAIR AND URINE OF PERSONS WORKING IN, OR IN CONNECTION WITH, ARSENIC TRICHLORIDE PLANTS

Date[1]	Chemical Works	Name	Age	Nature of Work	Length of Time Employe.	Arsenic as Arsenic Trichloride in		Chemical Examination of Urine[2]				Remarks
Urine						Hair	Urine	Sp. Gr.	Reaction	Albumin	Indican	
9 15 17	chemical works, Widnes	H. H.	45	workman in plant	*months* 9	*mmg. per 100 gm.* 264,000	*mmg. per 100 c.c.* 220	1030.0	+3	1?	3	Employed in new plant since end of August or beginning of September; previously in old plant.
Hair												
9 12 17	same	" "	"	same								
10 10 17	"	" "	"	"	10	500,000	80	1031.2	+2	0	1.2	
Urine												
12 26 17	"	" "	"	"	12	6,000	under 10	1026.0	+2	0	3	Taken after the man had been several weeks at Blackpool on holiday.
Hair												
12 31 17	"											
Urine												
9 15 17	"	W. G.	35	"	9	378,000	250	1027.0	+3	1?	—	Employed in new plant since end of August or beginning of September; previously in old plant.
Hair												
9 12 17												
10 22 17	"	" "	36	"	10	600,000	80	1022.0	+3	0	1?	
Urine												
12 26 17	"	" "	"	"	12	25,000	under 10	1028.0	+2	1?	2	Taken after the man had been several weeks at Blackpool.
Hair												
12 31 17												
1 17 18	"	J. M.	—	"	12(?)	300,000	30	1018.0	+2	0	0?	Dermatitis—arsenical?
1 17 18	"	S. L.	—	"	12(?)	240,000	5	1017.0	+2	0	0?	R and necrosis.
1 15 18	"	—. H.	—	chemist[3]	12(?)	280,000	—	—	—	—	—	
10 8 17	laboratory of chemist	P. K.	30	"	18	80,000	10	1016.0	+2	—	1	
11 23 17	inspection department	" "	"	"	19½	60,000	10	1016.0	+1	0?	0	Has not been well.
1 29 18	same	" "	"	"	21½	8,000	10	1022.0	+1	0	1?	About six weeks after short holiday.
10 8 17	"	J. S. J.	20	"	2	70,000		1015.0	+2		1	
11 23 17	"	" "	"	"	3½	45,000	10	1031.0	+3	1?	0?	
1 29 18	"	" "	"	"	5½	10,000	25	1028.0	—	1?	1	
11 27 17	chemical works, Gateshead	J. A.	28	workman in plant	3	22,500	under 10	1023.0	+2	1?	1?	
11 27 17	same	J. B.	33	same	3	75,000	" 10	1013.0	+2	0	0?	

[1] Arrangement of dates follows the American custom—*i.e.*, month, day of month, year.

[2] 1=slight or scant; 2=moderate; 3=strong or abundant. A material amount of arsenic was found in the urine only in the cases of the workmen H. H. and W. G., and was associated with marked excess of indican on three occasions.

[3] The chemists were exposed to the fumes of arsenic trichloride in connection with the sampling and the analysis of the product. Mr. H. was in addition exposed to fumes from the retorts while supervising the workmen.

rate pipes. The hydrochloric acid was conveyed away by a drain, and the arsenic trichloride was carried down a pipe to a collecting pipe which emptied into a large tank. A tap near the bottom of this tank was used to fill the iron barrels.

The salt and the arsenic trioxide were mixed by men on the mixing platform just before being shovelled into the retorts. The lid of the charging hole of the retort was unsealed just before this operation, and the fumes from the retort and the dust from the chemicals were carried down into the retorts by an induced downward draft. To protect themselves against dust, the men wore handkerchiefs over the mouth and nose. Gas helmets were also available.

At the time of this visit, three of the retorts were working—one of the old type (retort 4) and the two new type retorts (5 and 6). From these three retorts a considerable amount of irritating fumes escaped at various places. This was most noticeable in the neighborhood of the pipe rising from retort 4. It appeared also that escape was taking place through the sulphuric acid seals guarding a lateral valve and, in all probability, some escaped also from the drain carrying away the waste hydrochloric acid. A strong odor was also noticeable in the neighborhood of the storing tank, and more particularly near the outlet tap. Although there was a fairly strong wind at the time of the visit, a very distinct odor, which resembled that of hydrochloric acid but differed materially from it, was noticeable in every part of the installation. This odor was strongest on the upper platform near the retorts, particularly near the old retort.

Three pairs of test plates were exposed as follows: two plates at the level of the ground at a distance of about 2 feet from one side of the vertical pipe going to the condenser from retort 4, and about 3 feet away from the charging hole of the retort; two plates in a corresponding position near retort 5, but at a height of 19 inches; and two plates near retort 6, in a similar position, but at a height of 9 inches.

These plates were left from 2 P. M. on December 19, 1917, until the same hour on December 20. They were then replaced by three similar sets of plates which were left exposed in the same way for 24 hours and taken up on December 21. During each of the exposures the retorts were charged once. At the end of the exposure, each pair of plates was carefully packed and forwarded to the laboratory.

On arrival at the laboratory these plates presented a very striking appearance. The two sets of plates which had been exposed near retort 4 were thickly encrusted with a sulphur-yellow, saline-looking deposit, which could be scraped off with difficulty. When water was added the yellow color diminished or disappeared for a short time, and then gradually reappeared. On the addition of potash the color deepened and became brownish, and after an interval a brownish-red precipitate separated. (The color was apparently due to the presence of some iron chloride.)

The deposit on the plates exposed near retort 6 was much less abundant than that on the plates near retort 4, and was not so yellow. The plates near retort 5 also had a very distinct deposit, but this was much less abundant than that on the plates exposed near retort 6. All these deposits were dissolved in a dilute potash solution and the amount

of arsenic was estimated both by the iodine method and the hydrochloric-copper method with the results shown in Table 6.

The differences between the results obtained are puzzling, and are probably due to the fact that it was found difficult

TABLE 6.—TOTAL ARSENIC (AS ARSENIC TRIOXIDE) DEPOSITED ON PLATES 138 MM. IN DIAMETER

A. Estimated by Iodine Method

Position of Plates	Twenty-Four-Hour Exposure, Dec. 19-20	Twenty-Four-Hour Exposure, Dec. 20-21
	mmg.	*mmg.*
Near retort 4, at level of floor	341,000	39,600
Near retort 5, 19 inches high	6,930	4,950
Near retort 6, 9 inches high	5,940	17,820
B. Estimated by Hydrochloric-Copper Method		
Near retort 4, at level of floor	200,000	180,000
Near retort 5, 19 inches high	8,300	4,000
Near retort 6, 9 inches high	16,000	50,000

to obtain clear solutions. Filtration was obviously contraindicated. It is probable also that something interfered with the action of the iodine. The solutions were thoroughly shaken to equalize the distribution of any undissolved parts, but this obviously was insufficient. Two points are clear, however—namely, that a material amount of arsenic could be obtained from the air in the neighborhood of each of the retorts, and that the air near the old retort was laden to a much greater extent than that near the new retorts.

Protection of Workmen against Arsenic Trichloride Fumes

When about 1 gm. of arsenic trichloride, with a surface of approximately 7 cm. square, is allowed to evaporate in 20,000 c.c. of still, moderately dry air, about 0.18 gm. of the fluid is volatilized during the first hour, and 0.4 gm. during the following twelve hours. Broadly speaking, about half of the arsenic trichloride is volatilized during the first twelve hours.

If the precipitate which forms in the air charged with this vapor is collected on test plates, the distribution of the fumes can be ascertained. In one experiment 0.25 c.c. of arsenic trichloride was allowed to evaporate in the comparatively dry still air of the 215,000 c.c. chamber. The fluid was placed at a height of 20 cm. above the floor of the chamber. One test plate was placed at a height of 20 cm. vertically above, and another 20 cm. below the arsenic trichloride. A third plate was placed at a distance of 50 cm. from plate 1 and at the same level; plate 4 was placed at the same distance from plate 2 and at the same level. At the end of six and three-quarters hours all the test plates were removed. The appearance of these plates and the amount of arsenic recovered from each of them are indicated in Table 7.

After the four test plates had been removed, a fifth test plate was fixed in the chamber in the same position as that occupied previously by plate 1. The chamber was closed again, and opened only after an interval of four days. At the end of that time there had formed on the plate a thin crystalline deposit which also contained arsenic. The amount and distribution of the deposit is very much affected by driving air laden with arsenic trichloride through suitable channels, as is shown by the following experiments for which the chamber used in the previous experiment was employed.

The fumes were carried into the chamber by a current of air which had been passed over arsenic trichloride.

This current was admitted at one end of the chamber by a tube having a sectional area of about 1 cm. square. An equal amount of air was removed from the other end of the chamber by a tube of the same diameter. Test plates were placed: (1) about 10 cm. below the inlet pipe; and (2) about 30 cm. vertically above the inlet pipe. After 10,600 c.c. of air had passed through the chamber in the course of sixty-five minutes, it was found that 0.42 gm. of arsenic trichloride had been taken up by the 10,600 c.c. of air. Both test plates were covered with a dense white deposit, particularly plate 1. The amount of arsenic recovered from plate 2 was 544 mmg.

The inlet pipe which was turned upward was now partly covered with a ventilating hood formed by a glass cylinder 3 cm. in diameter connected by four tubes with the outlet tube, so that the air charged with arsenic trichloride was thrown into the hood-like cylinder instead of being admitted freely into the chamber. In every other respect the experiment was conducted exactly in the same way as the previous one—*i.e.*, 10,600 c.c. of air charged with arsenic trichloride were carried into the chamber and an equal amount withdrawn through the four ventilating tubes. At the end of sixty-five minutes the deposit on plates 1 and 2 was very scanty. A small number of crystalline particles were deposited on plate 1, and a still smaller number on plate 2. The amount of arsenic recovered from plate 2 was 198 mmg.—*i.e.*, about one-third of the amount which had been recovered from the plate in the same position in the first experiment. This experiment was repeated with a current of air dried over sulphuric acid, with a similar result.

TABLE 7.—RESULT OF EXPOSURE OF PLATES IN ATMOSPHERE CHARGED WITH ARSENIC TRICHLORIDE FUMES

Plate No.	Position in Relation to Arsenic Trichloride	Appearance of Deposit		Arsenic as Arsenic Trioxide Recovered from Each Plate
		By Reflected Light	By Transmitted Light under Microscope	
				mmg.
1	20 cm. vertically above	opaque white, dense	semi-crystalline granules, very abundant and large	6,400
2	20 cm. vertically below	grayish white, less dense	semi-crystalline granules, less abundant than on plate 1	3,200
3	20 cm. above and 50 cm. to one side	whitish gray	smaller and less abundant than on plate 2	2,400
4	20 cm. below and 50 cm. to one side	whitish gray	same as plate 3	2,400

A considerable amount of fumes had, therefore, been removed by the ventilating tube, but as the cylinder which served as a hood was freely open at the bottom, some heavier parts of the fumes had not been carried away. The velocity of the air passing through the ventilating hood was only about 23 cm. per minute.

These preliminary experiments showed that, in order to prevent the passage of arsenic trichloride into the air, a ventilating hood open at the bottom, though useful, was not sufficient. The tendency which the greater part of the fumes have to rise even when helped by an ascending draft of moderate velocity is not sufficient to prevent the contamination of the air by the fumes which have a tendency to take a down-

ward direction. Although it seemed probable that this difficulty could be overcome by having resort to a draft of greater velocity, it appeared desirable to devise a less expensive method.

With this object, the apparatus shown in Figure 7 B was constructed. This consisted of a bell jar 22,000 c.c. in capacity, in which was suspended a glass

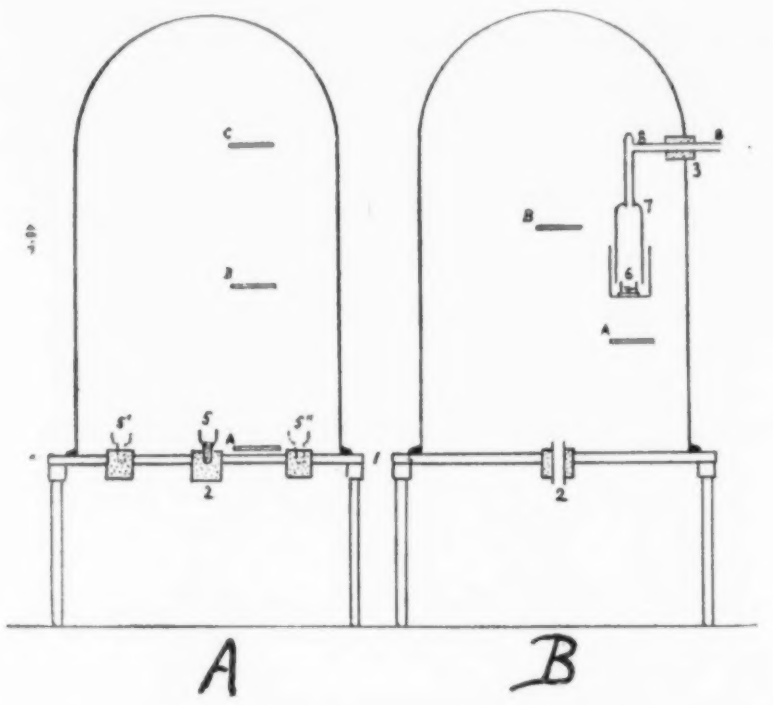


FIG. 7A.—Bell jar arranged for studying production and removal of arsenic trichloride fumes. (Scale 1 to 13.)

1=base glass plates. One of plates has only one central hole 2; the other plate has two holes. (In diagram A the three holes have been represented diagrammatically as in one plate.) 2=central opening closed by cork holding small cup 5 containing arsenic trichloride. This may be replaced after a short time by a similar cork with a small cup containing water, ammonia, or other chemicals. 5′ and 5″=two cups used in experiments in which arsenic trichloride and some other products were exposed simultaneously. A, B, and C=test plates.

B. Arrangement adopted in ventilation experiments. 6=capsule containing arsenic trichloride resting on bottom of outer cylinder. 7=inner cylinder acting as ventilating hood. 8=outlet tube connected with aspirating flask.

cylinder, 7, serving as ventilating hood open at its lower end and connected at its upper end with an outlet or ventilating tube. The vessel containing arsenic trichloride, 6, was placed at the mouth of this ventilating hood in the bottom of a cylindrical vessel of larger diameter than cylinder 7; the lower end of this external vessel was closed and its sides rose about halfway up the ventilating hood which was, therefore, surrounded by an outer cylinder, the mouth of which was directed upward, so that when a current of air passed from the large chamber to the outlet tubes it was forced first to flow downward toward the mouth of the hood ascending through the hood itself.

The following experiment was made with this apparatus:

After about 1.5 gm. of arsenic trichloride had been dropped into capsule 6 through tube 8, the tube was connected immediately with an aspirator and air was made to pass through the system at the rate of 500 c.c. per minute. Some ammonia was then introduced through opening 2 in the bell jar. Almost immediately dense white fumes were observed in the hood (cylinder 7) and in the outlet tube, as well as in the lower part of the outer cylinder guarding the mouth of the hood. The air of the jar remained quite clear, and the test plates A and B remained bright and apparently free from deposit.

When the jar was opened at the end of twenty minutes the test plates examined under the microscope appeared to be free from deposit, but a distinct trace of arsenic was detected on chemical analysis of the washings of the plates.

Fresh test plates were then introduced under the bell jar, and the ventilating apparatus was disconnected from the aspirator, and the chamber left unventilated for twenty minutes. At the end of this time the test plates were found to be covered with a scanty white deposit and their washings contained 178 mmg. of arsenic (as arsenic trioxide).

As these results were not quite satisfactory, it appeared desirable to take advantage of the action which water,

or water vapor, has upon arsenic trichloride. In order to do this the bottom of the outer cylinder was covered with a thin layer of water over which the air admitted to the hood 7 was forced to pass. The ventilating tube outlet 8 was then connected with a water pump, and the amount of air passing through the chamber and the hood measured by means of a gas-meter. As in the previous experiments, test plates were placed below and at the side of the hood covering the arsenic trichloride. The experiment lasted three hours and fourteen minutes, during which time 244,000 c.c. of air passed through the ventilating apparatus, or on an average 1,250 c.c. per minute. The area of the space between the inner and outer cylinders being 7.8 cm. square, the velocity of the air entering the hood was about 160 cm. per minute. The temperature of the air was 16°C. The amount of arsenic trichloride evaporated was about 0.4 gm. At the end of the experiment the test plates were quite clear and their washings contained no appreciable amount of arsenic.

For control purposes test plates were exposed in the same chamber, after the hood had been lifted several inches above the arsenic trichloride, and after the lower cylinder with the thin layer of water at the bottom had been removed from under the arsenic trichloride and placed at some distance from it. After these alterations a current of air was made to pass through the chamber for two hours at the same rate as before. (This was discontinued during the third hour.) After three hours' exposure in the chamber there was a distinct deposit on the plates, the washings of which yielded 360 mmg. of arsenic.

This last experiment shows how arsenic trichloride fumes can be prevented from contaminating the air around retorts, conduits, tanks, etc. At the same time, special ventilating arrangements are needed to remove fumes which arise when arsenic trichloride is necessarily exposed to the air in the filling of drums or the sampling of their contents. Air containing fumes so removed could be purified by a fine water spray before being discharged in the atmosphere. All persons employed on this work should wear some impervious general clothing, and only experience can show whether they should not also wear suitable gas masks.

Some Effects of Personal Accidental Exposure to Arsenic Trichloride

The experimenters sustained accidental local and general exposure in the laboratory and when visiting the works in the course of this inquiry. On two occasions small necrotic lesions of the epidermis were experienced, which resembled those obtained experimentally with animals.

Exposure to fumes was followed by pharyngeal and laryngeal irritation, headache, giddiness, nausea alternating with feelings of excessive hunger (gastric irritation), abdominal discomfort, pains in the thighs, legs and feet, and edema of the feet. At the same time the urine, which normally contained as a maximum 5 mmg. of arsenic trioxide per 100 c.c., was found to contain 20 mmg.

These personal experiences confirmed the results of the experiments and assisted in their interpretation.

Summary

A worker employed in the manufac-

ture of arsenic trichloride, upon whose leg this chemical was spilled, died of acute arsenicism; and others so employed were found to be exposed to risk of poisoning.

The hydrochloric-copper and the iodine volumetric methods of estimating the presence of arsenic, which were used in this inquiry, are described. Arsenic was found in the hair and urine of persons and animals exposed to arsenic trichloride fumes.

Inunction and inhalation experiments on animals are described. In both series of experiments death due to arsenical poisoning followed.

Water vapor was found to decompose arsenic trichloride, forming a light precipitate of oxychloride.

The air of places where arsenic trichloride was prepared or handled was found to contain arsenic compounds, and arsenic was found in the hair and urine of men employed.

Risk of poisoning can be avoided by providing with a water seal all places from which arsenic trichloride can possibly escape.

The experimenters themselves experienced local and general symptoms of poisoning during the inquiry.

BOOK REVIEWS

TUBERCULOSIS AND THE COMMUNITY. By *John B. Hawes, 2d*, M.D., Director, Clinic for Pulmonary Diseases, and Assistant Visiting Physician, Massachusetts General Hospital; Instructor, Graduate School of Medicine, Harvard University; Consultant in Diseases of the Lungs, New England District U. S. Veterans' Bureau; President, Boston Tuberculosis Association; Member, National Tuberculosis Association, Massachusetts Tuberculosis League, etc. Cloth. Pp. 168 with preface and index. Philadelphia and New York: Lea & Febiger, 1922.

This monograph deals with the problem of tuberculosis as it affects the whole community, rather than with tuberculous disease in the individual. It is written in a clear, simple, forceful style and in language readily intelligible to the layman interested in tuberculosis as a social problem. The brevity of the monograph, its clear presentation of scientific facts, and its readable character make it a useful book for teachers of hygiene to recommend to their students.

Chapters are devoted to the frequency, the transmission, and the cost of tuberculosis; to the care of consumptives; to tuberculosis and its relation to schools and schoolchildren; to tuberculosis and housing; to tuberculosis and occupations; to the careless and incorrigible consumptive; to the tuberculosis program for small cities and towns; and to the present needs of the tuberculosis campaigns. —*Katherine R. Drinker.*

PUBLIC RELIEF OF SICKNESS. By *Gerald Morgan.* Cloth. Pp. 195 with index. New York: The Macmillan Company, 1922.

This book is perhaps not intended for the general public nor even for the medical profession as a whole; but rather for thinking citizens of all classes who can believe that it is possible by legislative measures to abolish the poverty arising from disabling illness, and to provide adequate medical care. It is simply and thoughtfully written, and lucid in outline and development.

The author's thesis is that heretofore legislation has been more or less unsuccessful, because of the attempts to cover cash benefits and medical treatment by a single legislative proposal. He begins with a discussion of the complex relation between sickness and poverty, and, quoting conservatively from the Report of the Health Insurance Commission of the State of Illinois, shows that roughly 25 per cent. of social degradation is due to illness among the workers whose income is on the edge of the deficiency limits. In the next chapter he considers the opportunity for satisfactory medical treatment available to the person of moderate means, and he finds that it is very rare except in the large centers. Only in the pay clinics with paid personnel is it satisfactory with regard to the specialties and to self-respecting relations between patient and physician. The amount

of insurance against illness in this country is insufficient and limited to fraternal orders, to workmen's societies of unions or foreign groups, or to establishment (factory) funds. It is rarely carried with commercial carrier.

The author shows how solution of the problem has been attempted: first, in Denmark by state encouragement and subsidy of voluntary associations which now include 30 per cent. of the population. In an endeavor to extend this service, however, the dues have been made so low as to allow only meager sick benefit payments and limited medical service. In Germany the compulsory insurance is administered by local funds paid partly by the employer and partly by the employee, but in poorer communities where wages are low medical service and benefit payments are small. There have been many doctors' strikes. The benefits paid are half the weekly wage; and for the poor this is inadequate. There is no medical service to the families of the insured.

The English system is a compromise between older workmen's societies, Poor Laws of Relief, government, and medical interest. It is administered by two forms of organization; the first cares for the cash benefits, the other for medical treatment. The expense is shared by workman, employer, and government. Cash benefits are the same for all men but for women they are somewhat lower. Medical benefits are provided without cost to the worker. The panel doctor is paid per capita, and hasty work is encouraged. No allowance is made for special examination or treatment.

In the author's opinion all the above attempts fail by trying to include cash relief and medical aid in a single legislative measure. It is possible to calculate the amount of cash required for benefits in a large group by means of life insurance actuarial tables; but the cost of sickness, with constantly changing medical technic, cannot be calculated.

In New York, legislation was proposed which would provide cash and medical care to all, except agricultural and domestic workers. This was based on a maximum wage of $12, which is very low; but it lessened the burden of the low wage earner by throwing the full cost of insurance on the employer who paid less than $5 per week. The system was to be administered by Associations (Funds) composed of and managed by employers and their employees, under state supervision. Medical care was included. It is the author's opinion that by eliminating the medical benefits altogether, cash benefits could be raised to an adequate amount without extra expense—the cost to be about 1 1/3 per cent. of total wages.

Medical care should, then, be provided by health centers with paid staff and workers. Where localities are unable to finance these themselves, the state should aid them; but these centers would be the property of the community and would furnish scientific medical care to all classes of taxpayers at a reasonable price.—*J. W. S. Brady.*